DOI: https://doi.org/10.2298/SARH210508076S
UDC: 615.211.03

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Impact of ketamine on spontaneous coordinate activity and short memory behavior in rodents' chronic unpredictable stress model

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SUMMARY

Introduction/Objective This research aims to evaluate the impact of chronic stress on behavioral effects of ketamine, which are still not sufficiently clear.

Methods Wistar male rats aged five weeks were used in the experiment. The animals were divided into two equal groups: control and experimental. After being exposed to a chronic unpredictable stress paradigm for 42 days, experimental rats received a single injection of ketamine (10 mg/kg; day 45) as did the control group. The impact of ketamine was assessed using behavioral tests, spontaneous coordinate activity, and water maze tests for the evaluation of short-term memory.

Results The experimental group rats showed less spontaneous motoric activity than before ketamine application. Statistical significance was shown in gaining weight after time of ketamine application in the control group, as well as in the experimental group, where they showed weight loss during stress paradigm and then increased their weight after ketamine application. There was no statistical significance in speed measurements in either group, showing no effects on short-term memory behavior.

Conclusion These findings show that ketamine in a single subanesthetic dose has antidepressant and anxiolytic-like effects in male rats exposed to chronic unpredictable stress paradigm.

Keywords: Wistar rat; chronic unpredictable stress paradigm; ketamine; behavior

INTRODUCTION

Anxiety presents a normal reaction to various stressful events and is most often very useful in some situations, by helping one prepare for potential danger and inducing one's adequate reaction. Anxiety disorders refer to anticipation of future concerns and doubts, fear and avoidance. They also present the most common group of mental disorders generally nowadays [1]. Drugs that affect the serotonergic and GABAergic neurotransmission are often used in treatment of stress disorders but also show some limitations in their use, aiming further investigations in other direction [2]. A great potential of different negative glutamate transmission modulators has been shown as a result of many studies [3, 4]. Ketamine presents a dissociative anesthetic, non-competitive N-methyl-D-aspartate receptor antagonist with rapid and sustained anxiolytic and antidepressant effects manifested in clinical and preclinical studies lasting for a couple of weeks, which means that probably even a single dose of ketamine might have beneficial effects on anxiety conditions [5]. There is significant discrepancy among preclinical studies related to anxiolytic effects of ketamine. There are also different profiles of ketamine that make an impact in animal tests concerning anxiety/stress/fear, which much depend on the experimental paradigm, schedule of ketamine application, doses, and tested animals. Initially proposed as a depression model, chronic unpredictable stress paradigm (CUS) is a widely used paradigm in investigating stress disorders in preclinical research in rodents. It comprises continuous and consecutive exposures to variable, unpredictable, and aversive stressors lasting for weeks [6]. Many already conducted studies showed great similarity of paradigm variables to chronic stressful conditions of human life as well as decreased locomotor and exploratory activity and impaired learning and memory as one of the signs of anhedonia after CUS paradigm was completed [7].

This research aims to evaluate the impact of chronic stress on behavioral effects of ketamine. The objective of this study was to investigate the impact of chronic stress on tested animal behavior after ketamine was applied and whether ketamine could improve anxiety-like behaviors seen in rats exposed to chronic unpredictable stressors and to determine possible variations.

METHODS

Wistar male rats (250–300 grams; Faculty of Medicine, University of Belgrade), aged five weeks (approximates time of adolescence in

Received • Примљено: May 8, 2021
Revised • Ревизија: August 24, 2021
Accepted • Прихваћено: August 30, 2021
Online first: September 3, 2021

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humans), were used at the beginning of the experiment. They were allowed one week acclimatization period before unpredictable stress exposure. There were 16 rats in total, kept in Makrolon cages, two animals per cage, and fed *ad libitum* with a full rat mixture formula (Veterinary Institute, Subotica); water used for the animals was from the Belgrade water supply; room temperature was 22 ± 2°C, following the 12 to 12 day and night regime. At the beginning of the experiment, the animals were divided into two equal groups: control and experimental, each containing eight rats. The control group was kept and fed as previously specified. The experimental group was exposed to continuous stress during 42 days according to the following schedule: on day one, the animals were transferred from one cage into the other, so that the pairs from the beginning of the experiment are separated; on day two, the animals were exposed to 24-hour light; on day three, they were retransferred to separate the previously formed pairs; on day four, the animals were subjected to tail clipping by taking the tip of the tail with a clamp, lifting the animal 20 cm above the cage where it was kept for 15 seconds and returned back to the cage; on day five, the animals were retransferred to separate the previously formed pairs, and on day 6, they were deprived of food and water during 24 hours. That cycle was repeated until day 42 from the beginning of the experiment. [8, 9]. After 42 days from the beginning of the experiment, the animals were exposed to behavioral tests as follows: observation of spontaneous activity in the new space and testing short-term memory in a water pool without any previous treatment, following intraperitoneal administration of 10 mg/kg ketamine hydrochloride and 20 minutes after ketamine was applied, observation of spontaneous activity and short-term memory testing in a water pool. The control group was allowed usual animal activities and was subjected to the same tests, and ketamine was administered in the same dose. After testing, all animals were tested for glucose levels. The weighing of animals was performed three times. The first weighing was during the stress paradigm, the second one was performed seven days after, before ketamine application, and third weighing was also six days after the second weighing.

All experiments were carried out according to the NIH Guide for Care and Use of Laboratory Animals and were approved by the Ethics Committee of the University of Belgrade (permit number 513/1, 27.01.2020).

Spontaneous activity

Spontaneous activity of the rats was measured on the 43rd day using an Ugo Basile Activity Cage 7401 device. The rats were placed into the device individually and kept there for two hours, during which time the number of spontaneous movements was measured at five-minute intervals.

Short-term memory

Short-term memory and spatial navigation learning were tested on the 44th day using a 25°C, circular, 40-cm deep water pool; in one quadrant of the pool there was a rectangular 15 × 15 cm "island" with surface 1 cm below the surface of the water. The animals were prepared the previous day by being placed into the water and slowly directed to swim towards the "island." If a rat did not locate the platform after 90 seconds, it would be guided to the platform and allowed to remain on the platform for 20 seconds to recognize the location. The rats received three such consecutive trials on the day before the testing day with an intertrial interval of 30 seconds. The water was changed each day. The escape latency time for the rat to locate and climb onto the platform was observed and recorded. For each trial, the rats were allowed to search for the hidden platform for a 90-second period. The day after the preparation, the procedure was repeated, the time elapsed from placing an animal into the water until it found the "island" and climbed onto it was measured by a chronometer. On the 45th day, the same procedure was repeated, but this time 20 minutes after ketamine administration. This test was used to measure spatial navigation learning and short memory in rats. Both groups of rats were trained for one day, and the swimming test was performed as described previously [10].

Statistical analysis

All observed data have normal distribution, so that the following parameter tests were performed: the parameter paired t-test within groups and the parameter matched t-test for comparing pair times. In addition, Pearson's correlation was used in order to establish the degree of linear connection.

RESULTS

Comparison of successive times in spontaneous activity measurement in the experimental group before and after ketamine application was performed in this experiment. The same procedure was performed within the control group. The differences between time parameters between the experimental and the control group were not calculated as we aimed to examine the behavior in each group independently, to show the effects of ketamine on the animals' behavior.

Before ketamine application in the experimental group, the results showed statistical significance in time windows between the fifth and the 10th minute, the 10th and the 15th, the 15th and the 20th, and the 55th and the 60th minute. In the control group, the statistical significance was shown in successive time windows between the 15th and the 20th minute and the 50th and the 55th minute (Table 1 and Figure 1).

After ketamine application in the experimental group, the statistical significance was shown in time windows between the 15th and the 20th minute and the 25th and the 30th minute. In the control group, the statistical significance was shown between the 10th and the 15th minute and the 35th and the 40th minute (Table 2 and Figure 2).

Table 1. Succeeded time comparison in control and stress groups before treatment

Paired samples statistics		Control group			Stress group		
		Mean	SD	p	Mean	SD	p
Pair 1	Time5	144.67	82.641	0.535	241.38	43.041	**0.006**
	Time10	126.5	42.627		164.38	44.397	
Pair 2	Time10	126.5	42.627	0.235	164.38	44.397	**0.014**
	Time15	97.83	16.278		118.63	49.753	
Pair 3	Time15	97.83	16.278	**0.000**	118.63	49.753	**0.015**
	Time20	73.17	17.429		79	35.505	
Pair 4	Time20	73.17	17.429	0.336	79	35.505	0.698
	Time25	63	21.457		76.88	39.948	
Pair 5	Time25	63	21.457	0.809	76.88	39.948	0.179
	Time30	57.67	61.617		56.75	29.085	
Pair 6	Time30	57.67	61.617	0.850	56.75	29.085	0.130
	Time35	62.17	33.772		42	22.552	
Pair 7	Time35	62.17	33.772	0.563	42	22.552	0.570
	Time40	54.17	39.686		36.25	20.852	
Pair 8	Time40	54.17	39.686	0.116	36.25	20.852	0.623
	Time45	33.67	24.476		42	19.198	
Pair 9	Time45	33.67	24.476	0.372	42	19.198	0.358
	Time50	48	20.794		33.5	24.378	
Pair 10	Time50	48	20.794	**0.008**	33.5	24.378	0.292
	Time55	24.5	18.982		25.75	18.352	
Pair 11	Time55	24.5	18.982	0.826	25.75	18.352	**0.025**
	Time60	22.83	16.29		48.5	28.122	

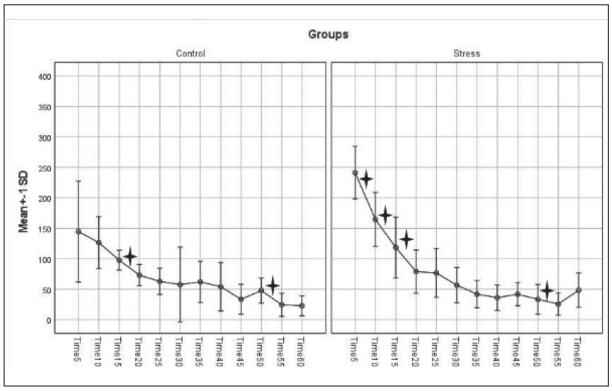

Figure 1. Successive times in spontaneous activity measurement in experimental group before ketamine application

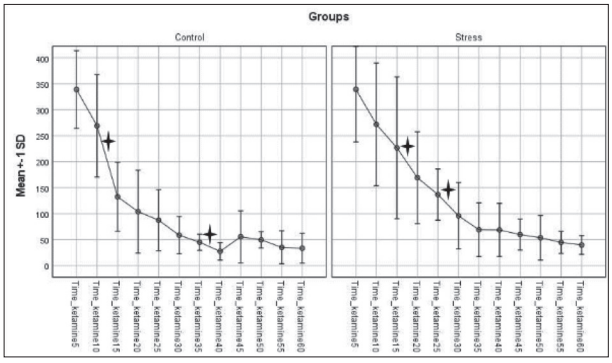

Figure 2. Successive times in spontaneous activity measurement in experimental group after ketamine application

After ketamine was applied, the experimental group showed less spontaneous motor activity than before ketamine was applied.

The control group showed weight gain after ketamine was applied and experimental group showed weight loss when stressed, during CUS paradigm, but also weight gain after ketamine was applied (Figure 4 and Table 3).

There was no statistical significance in speed measurement in both groups.

The glucose level of the control group was elevated as late as 30 minutes after the baseline and then returned to normal. As for the stress group, it can be seen that the glucose level rise was abrupt and differed compared to the baseline and then dropped after 30 minutes. Statistically significant rise/drop was observed almost at all measured times (Figure 3 and Table 3).

Table 2. Succeeded time comparison in control and stress groups after treatment of ketamine

Paired samples statistics		Control group			Stress group		
		Mean	SD	p	Mean	SD	p
Pair 1	Time_ketamine5	339	74.825	0.068	339.25	101.064	0.099
	Time_ketamine10	269.17	98.493		271.88	118.082	
Pair 2	Time_ketamine10	269.17	98.493	**0.005**	271.88	118.082	0.186
	Time_ketamine15	132.5	66.443		226.75	136.581	
Pair 3	Time_ketamine15	132.5	66.443	0.074	226.75	136.581	**0.056**
	Time_ketamine20	104	79.815		169.25	88.286	
Pair 4	Time_ketamine20	104	79.815	0.270	169.25	88.286	0.271
	Time_ketamine25	87.5	58.76		136.75	49.204	
Pair 5	Time_ketamine25	87.5	58.76	0.271	136.75	49.204	**0.014**
	Time_ketamine30	58.67	35.943		96	63.933	
Pair 6	Time_ketamine30	58.67	35.943	0.407	96	63.933	0.102
	Time_ketamine35	45	15.427		69	51.758	
Pair 7	Time_ketamine35	45	15.427	**0.012**	69	51.758	0.980
	Time_ketamine40	27.5	16.814		68.63	51.264	
Pair 8	Time_ketamine40	27.5	16.814	0.189	68.63	51.264	0.477
	Time_ketamine45	55.5	50.007		59.75	29.793	
Pair 9	Time_ketamine45	55.5	50.007	0.800	59.75	29.793	0.561
	Time_ketamine50	49.67	15.565		53.63	42.915	
Pair 10	Time_ketamine50	49.67	15.565	0.286	53.63	42.915	0.625
	Time_ketamine55	35.17	31.884		44.75	21.346	
Pair 11	Time_ketamine55	35.17	31.884	0.937	44.75	21.346	0.693
	Time_ketamine60	33.5	28.829		39.75	18.077	

DISCUSSION

We investigated the effects of ketamine on spontaneous locomotor activity and short memory in rats within the CUS model. Spontaneous locomotor activity was measured in an activity cage; recording values which indicate pulses were recorded by the apparatus as the stainless bars tilted in response to animal movements, and activity of each rat was automatically recorded for consecutive five minutes. Our results showed an increase of spontaneous activity in both experimental and control groups of animals before ketamine was applied, in the time window between the 15th and the 20th minute and the 55th and the 60th minute of measurement, but at the beginning,

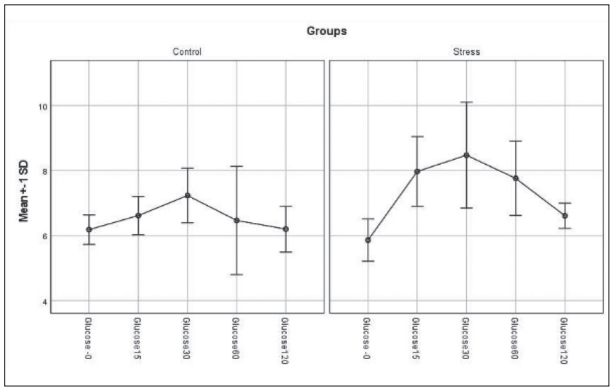

Figure 3. Glucose concentrations in the experimental and the control group

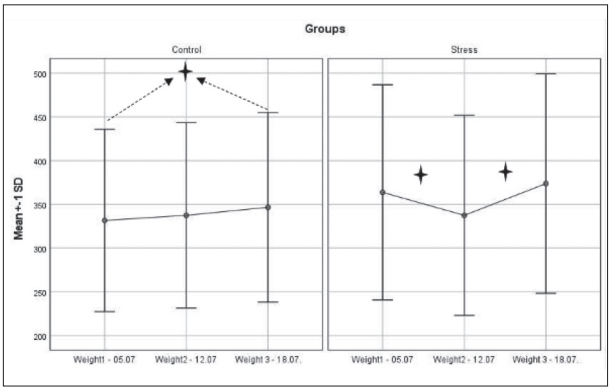

Figure 4. Weight changes in experimental and control groups in three time-point measurements

Table 3. Succeeded time comparison in control and stress groups for weight, speed, and glucose

Paired samples statistics		Control group			Stress group		
		Mean	SD	p	Mean	SD	p
Pair 1	Weight 1	331.667	104.195	0.201	363.75	122.962	**0.016**
	Weight 2	337.500	105.818		337.5	114.268	
Pair 2	Weight 1	331.667	104.195	**0.030**	363.75	122.962	0.353
	Weight 3	346.667	108.382		373.75	125.235	
Pair 3	Weight 2	337.5	105.818	**0.006**	337.5	114.268	**0.000**
	Weight 3	346.667	108.382		373.75	125.235	
Pair 1	Speed	15.5	9.203	0.177	9.5	8	0.779
	Speed ket.	8.5	4.231		8.625	4.868	
Pair 1	Glucose0	6.183	0.454	**0.056**	5.863	0.652	**0.001**
	Glucose15	6.617	0.591		7.975	1.071	
Pair 2	Glucose0	6.183	0.454	**0.027**	5.863	0.652	**0.006**
	Glucose30	7.233	0.838		8.475	1.627	
Pair 3	Glucose0	6.183	0.454	0.689	5.863	0.652	**0.001**
	Glucose60	6.467	1.665		7.763	1.143	
Pair 4	Glucose0	6.183	0.454	0.955	5.863	0.652	**0.026**
	Glucose120	6.2	0.704		6.613	0.387	
Pair 5	Glucose15	6.617	0.591	0.135	7.975	1.071	0.281
	Glucose30	7.233	0.838		8.475	1.627	
Pair 6	Glucose15	6.617	0.591	0.843	7.975	1.071	0.720
	Glucose60	6.467	1.665		7.763	1.143	
Pair 7	Glucose15	6.617	0.591	0.298	7.975	1.071	**0.013**
	Glucose120	6.2	0.704		6.613	0.387	
Pair 8	Glucose30	7.233	0.838	0.158	8.475	1.627	0.392
	Glucose60	6.467	1.665		7.763	1.143	
Pair 9	Glucose30	7.233	0.838	0.135	8.475	1.627	**0.020**
	Glucose120	6.2	0.704		6.613	0.387	
Pair 10	Glucose60	6.467	1.665	0.783	7.763	1.143	**0.018**
	Glucose120	6.2	0.704		6.613	0.387	

only the experimental group showed activity. These results showed immediate effects of CUS in the group of experimental animals as increased locomotor activity and as a result of anticipating pain and stress, which is in consistency with previously conducted investigations [11, 12, 13].

The experimental group rats showed less spontaneous motoric activity than before ketamine application, which shows longer term effects of ketamine administration and its anxiolytic effects as well, which was also shown in a study conducted by Bates and Trujillo [14], who also showed that repeated ketamine application might lead to addiction, with no statistical significance in cognitive deficits, memory, and spatial learning, which is in consistency with our findings related to the speed of swimming of animals and short-term memory, where we also found no statistical significance [14]. The inability of low ketamine dose to affect memory can be due to the short half-life of ketamine. At lower, subanesthetic doses, ketamine is able to mimic the effects of an antidepressant [15]. We administered ketamine at a single dose of 10 mg/kg, which was chosen as it is regarded to represent a recreational dose for use in rodents with LD50 of 600 mg/kg at four-hour intervals and was consistent with dosages reported in literature shown to be subanesthetic and primarily anxiolytic and antidepressant in rodents [16]. Noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists produce antidepressant effects after a single administration, which was shown at the forced swimming test and the tail suspension test. Research that included ketamine's antidepressant effects after acute single application showed that acute treatment with a noncompetitive NMDA channel blocker tends to improve depressive and anxiolytic behaviors induced by chronic stress [17]. Opposite to this, animals that were repeatedly administered ketamine demonstrated locomotor sensitization and addiction [18]. Previous research investigating the effectiveness of noncompetitive NMDA receptor antagonists has revealed inconsistent results. Recent research, however, has been providing robust evidence for ketamine's anxiolytic effects. In a study that investigated acute effects of NMDA receptor blockade with ketamine in an animal model of fear-conditioning affecting frequency and duration of freezing as well as associated neural changes in the subcortical structures, the results indicated that ketamine normalized stress-related depressive behaviors in areas associated with fear and anxiety [19]. Clinical use of ketamine, esketamine, has gained broad attention because of its rapid therapeutic effects, as well as effects that last for a significant amount of time after a single dose in treatment of depression-resistant patients [20]. As previously described, our investigation showed statistical significance related to weight was shown in the experimental group after stress paradigm (weight loss), after ketamine

application (weight gain) and between the first and the third weight measurement there were of no statistical significance. Our experimental group of animals showed weight loss due to the CUS paradigm, which confirms that these rats were in a state of anhedonia, one of the major signs of depression. Previous studies showed that chronic stress in the rodent stress animal model induces specific patterns of behavioral activity that indicate depression or anxiety, like anhedonia and loss of interest when exposed to behavioral tests [21]. The previous study of Cox et al. [22] also showed that the experimental group had slower weight gain even if the CUS model they used did not include food and water deprivation and increased locomotor activity noticed in behavior tests is proved not to be linked to this weight loss phenomenon. The weight measurement was done during the CUS, then after ketamine application (seven days after), and finally six days after the second measurement. There was no difference between the first and the third measurement, as experimental animals who were under stress events felt anhedonia and ate less, while after some time ketamine effects showed in weight gain. Even though stress enhances the response to insulin, our results showed that glucose level was significantly different and slower in its metabolism in the experimental group compared to the control group where its levels returned to normal after an hour. In the experimental group glucose levels remained higher than normal after the same period of time. Previous studies showed increased blood levels of glucose in rodents that were exposed to CUS and with ketamine application where short-term effect of ketamine was shown on regulation of body weight and food intake [23].

CONCLUSION

Our results clearly suggest that ketamine has anxiolytic properties on behavior at doses that do not produce short memory impairment but improve locomotor activity and weight gain. The anxiolytic effect of ketamine may be related to several neuromediator systems that are known to be involved in neuropharmacology of anxiety, such as serotonergic, glutamatergic, and GABAergic. Further research should elucidate the neuronal mechanisms that underlie specific differences in response to ketamine and highly specific mechanisms responsible for lasting, non-addictive effects on behavior.

Conflict of interest: None declared.

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Ефекти кетамина на спонтану координатну активност и краткорочну меморију у хроничном непредвидивом моделу стреса код глодара

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САЖЕТАК

Увод/Циљ Ово истраживање има за циљ да процени ефекте хроничног стреса на бихејвиоралне ефекте кетамина, који још увек нису довољно разјашњени.

Методе У експерименту су коришћени мушки пацови соја Вистар стари пет недеља. Животиње су подељене у две једнаке групе: контролну и експерименталну. Након што су били изложени парадигми хроничног непредвидивог стреса током 42 дана, експериментални пацови су примили једну инјекцију кетамина (10 *mg/kg*; 45. дан) као и контролна група. Утицај кетамина процењен је помоћу тестова понашања, спонтане координатне активности и тестова воденог лавиринта за процену краткорочног памћења.

Резултати Експериментални пацови су показали мање спонтане моторичке активности пре апликације кетамина. Повећање тежине је показано након апликације кетамина у контролној групи. У експерименталној групи је показан губитак тежине након парадигме стреса, а затим је показано повећање тежине након апликације кетамина. Није било статистичке значајности у мерењу брзине у обе групе, што указује да није било ефекта у краткорочној меморији.

Закључак Ови налази показују да једнократно примењен кетамин у субанестетичкој дози поседује антидепресивне и анксиолитичке ефекте код пацова мужјака изложеним парадигми хроничног непредвидивог стреса.

Кључне речи: Вистар пацов; парадигма хроничног непредвидивог стреса; кетамин; понашање