folia medica

Folia Medica 63(2):189-96
DOI: 10.3897/folmed.63.e53912

Original Article

Effects of the Antinociceptive Dipeptide L-Tyrosine-L-Arginine (Kyotorphin) on Motivation, Anxiety, and Memory in Rats

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Received: 4 May 2020 ♦ **Accepted:** 15 June 2020 ♦ **Published:** 30 Apr 2021

Citation: Angelova H, Krumova E, Dzhambazova E, Pechlivanova D. Effects of the antinociceptive dipeptide L-tyrosine-L-arginine (kyotorphin) on the motivation, anxiety, and memory in rats. Folia Med (Plovdiv) 2021;63(2):189-96. doi: 10.3897/folmed.63.e53912.

Abstract

Introduction: The endogenous dipeptide L-tyrosine-L-arginine (kyotorphin, KTP) is found in brain structures related to the processing of information for nociception, the control of emotions, and memory formation. Besides the antinociceptive effect of KTP, it has a mild protective activity against the deleterious influence of the brain hypoperfusion and streptozotocin on the behavior and memory.

Aim: We aimed to study the effects of the intracerebroventricular injection of effective antinociceptive doses of KTP on the motivational behavior, memory, and blood and hippocampal levels of the carbonylated proteins in healthy male adult Wistar rats.

Materials and methods: We used a paw-pressure test for assessment of acute nociception, an open field test for assessment of exploration and habituation to a new environment, elevated plus maze test for the evaluation of anxiety-like behavior, and novel object recognition test for working memory. Carbonylated protein assay was used for the assessment of the oxidative impairment of the proteins. The results were analyzed by ANOVA.

Results: The present data showed that all single doses of KTP exerted an antinociceptive effect, but this effect was not observed after chronic administration. Only the highest dose of 100 μg was able to induce anxiolytic and motor inhibiting effects. None of the doses used showed effects on the recognition memory or the level of the carbonylated protein.

Conclusion: Our results showed that KTP exerted its antinociceptive effect without affecting negatively the blood and brain carbonylated protein or basic behavioral parameters related to the exploration, motivation, and memory formation in healthy rats.

Keywords

anxiety, kyotorphin, memory, nociception, peptides

INTRODUCTION

The endogenous dipeptide L-tyrosine-L-arginine, whose structure is similar to that of endorphins, was discovered in Kyoto and named kyotorphin (KTP).[1] It was found in the brain cerebrospinal fluid of several species including humans.[1-4] KTP is unevenly distributed in the brain as the dorsal horns of the spinal cord, nuclei in the medulla oblongata, the pons, and midbrain structures, were found to be rich in KTP.[2] Accumulated evidence for the antinociceptive effects of KTP underlined its role in the processing of pain-related information in the above brain structures

interacting with the endogenous opioids.[5,6,8] However, approximately half of the endogenous KTP is distributed in the cerebral cortex, suggesting its potential to produce effects other than analgesia.[2] Relatively lower levels of KTP and its synthesizing enzyme were found in structures involved in the formation of different types of memory and the maintenance of fundamental body functions.[2,9] Existing data indicated that despite the use of the term "KTP receptor", such is not cloned and specifically isolated yet, which may assume the ability of KTP to bind not to a specific receptor but an oligomer formed by μ- and δ - opioid receptors.[10] Another suggested mechanism of action of KTP is its usage as a substrate for the synthesis of nitric oxide with further activation of the NO/cGMP pathway.[6] The imbalanced formation of NO can accelerate its interaction with the superoxide radical to form the powerful oxidant peroxynitrite which may produce post-translational carbonylation in endogenous proteins commonly occurred in the oxidative stress.[7] Additionally to its main antinociceptive activity, KTP has shown to exert neuroleptic, antiepileptic and neuroprotective effects.[8,12,13] Some KTP derivatives have been shown to prevent the cognitive impairment and neuronal damage in the hippocampus induced by chronic cerebral hypoperfusion and to suppress locomotors activity at a moderate rate.[14,15] The chronic intracerebroventricular (ICV) treatment with KTP displayed a mild protective effect on the deleterious consequences from an experimental model of Alzheimer's disease.[13,16]

AIM

In the present study, we aim to elucidate the role of ICV injection of effective antinociceptive doses of KTP on some basic parameters of the cognitive behavior like exploration, anxiety-like behavior, and habituation to a new environment, working recognition memory and on blood and brain levels of the carbonylated proteins.

MATERIALS AND METHODS

Animals, stereotaxic cannulae implantation and experimental design

Fifty adult Wistar male rats were implanted stereotaxically with cannulas under anesthesia (ketalar, 100 mg/kg, i.m., xylazine 5 mg/kg, i.p) in both lateral brain ventricles (AP = – 1 mm, L= 1.6 mm, DV = – 4 mm) using stereotaxic frame. The cannulas were fixed on the skull through screws and dental cement and the wound was closed.[17] The animals were kept in groups of 5 rats under standardized conditions: temperature 21±2°C, artificial light on 08:00-20:00 h, and fed with a regular rodent diet and tap water *ad libitum*. After a 5-day recovery period, the rats were randomly injected in one of the lateral ventricles (ICV) with kyotorphin (Sigma-Aldrich), dissolved in sterile artificial cerebrospinal fluid (CSF) at single doses of 25, 50, 100 μg/5 μl/rat or CSF (controls). One group was ICV injected sub-chronically with KTP at a dose of 100 μg/5 μl/rat/day for 10 days.

All experiments were carried out between 10:00 am and 1:00 pm during the autumn 15 – 20 minutes after the treatment with KTP in order: Open field, Elevated plus maze, Paw Pressure, Novel object recognition, Carbonylated protein assay. All experiments were approved by the Bulgarian Food Safety Agency (No 176/2019) which is under EC Directive 2010/63/EU for animal experiments.

Open field test (OFT)

The apparatus consists of an opaque box 100×100×60 cm. A digital camera was mounted above the test box and connected with the SMART video tracking system (Harvard Apparatus, US). Each rat was placed in the center and observed for 5 min. The habituation was estimated as total ambulation (trajectory length travelled for 1 minute during 5 min of observation).[12]

Elevated plus maze (EPM)

EPM comprised of two open arms (50×10 cm), provided with a small rim (1.5 cm), two enclosed arms (50×10×40 cm), and a central platform (10×10 cm). The apparatus was elevated 50 cm above the floor level. Each rat was placed on the central platform facing an open arm, and observed for 5 min.[18] The total trajectory travelled (in centimetres), and the ratio time spent in open arms/total time were recorded by SMART video tracking system and calculated in percentage.

Paw pressure test (PPT)

Accelerating mechanical pressure (in grams) was applied on the hind paw using an analgesimeter (Ugo Basile). The value needs to elicit nociceptive responses such as withdrawal or struggle was established as a mechanical pain threshold. The test was optimized by a single training of the animals without applying pressure 1 day before the experiments.[19]

Novel object recognition test (NORT)

The apparatus consisted of an opaque box 50×50×60 cm situated in a soundproof room. The procedure includes 3 phases: 1. The first day habituation to the empty box for 15 min; 2. The second day training – seconds for exploration of two identical objects; 3. The second day testing – 15 min after the training procedure the rats explore two objects, one familiar, (F) and one novel (N)) for 5 min. Objects do not have a resemblance to food and water and are cleaned after each test along with the whole box with alcohol to prevent odor traces. Discrimination of the N from F was

represented by a recognition index (RI) = Time exploring N×100% / (Time exploring N + Time exploring F).[20]

Carbonylated protein assay

We have used the assay for the detection of protein carbonyl groups that involve derivatization of the carbonyl group with 2,4-dinitrophenylhydrazine (DNPH), which leads to the formation of a stable dinitrophenyl (DNP) hydrazine product, which can be quantitated spectrophotometrically at 276 and 370 nm. The peak absorbance around 360 nm was calculated for the carbonyl content.[21] The total protein content was determined using the routine Lowry method[22], crystalline bovine albumin being a standard.

Statistical analysis

All data were analyzed by ANOVA (factors; factor Kyotorphin: a CSF and kyotorphin; factor Time: for OF test) and Bonferroni post hoc test. Differences with p<0.05 were considered statistically significant.

RESULTS

Fig. 1 shows that acute ICV injection of KTP at doses of 25, 50, and 100 μg/rat induced antinociception in PPT (F (3, 33) = 15.373, p<0.001). The sub-chronic treatment with the dipeptide at a daily dose of 100 μg/rat, however, did not change their normal pain threshold (H=0.121, p=0.728). EPM test data showed that all doses used had no impact on the total activity [F (3, 37) = 0.526, p>0.05] **(Fig. 2A)** and only a single dose of 100 μg/rat produced an anxiolytic effect increasing the ratio of time spent in the open arms of the maze [F (1, 21) = 4.199, p=0.054] **(Fig. 2B)**. The results from the OFT **(Fig. 3)** showed a significant time-dependent effect of all experimental groups [F (4, 174) = 23.882, p<0.001]. Controls demonstrated a normal decrease in the ambulation with time [F (4, 69) = 6.958, p<0.001]. KTP at a dose of 25 μg/rat did not influence the exploratory behavior as compared to the controls (p>0.05), but at a dose of 50 μg/rat decreased the motor activity at 5 minutes (t=2.571, p=0.012). KTP at a dose of 100 μg/rat provoked a significant diminishing in the activity [F (4, 109) = 6.146, p=0.015] at 4 and 5 minutes of the test (t=2.165, p=0.033; t=2.346, p=0.021). Sub-chronic KTP diminished the ambulation during all period [F (4, 104) = 44.111, p<0.001], but the pattern related to habituation was preserved (H=21.195, p<0.001). NORT also provides data for exploratory behavior. The time spent in sniffing the two new objects during the training phase of the test was significantly increased in rats, treated with a dose of 25 μg/rat [F (1, 19) = 8.027, p=0.011] **(Fig. 4A)**. Other doses have no effects on the exploration, and all doses used did not influence the normal working memory during the test phase (p>0.05) **(Fig. 4B)**. The analysis of the carbonylated protein in the blood plasma and isolated hippocampus showed that sub-chronic treatment with KTP did not change significantly the level of the impaired proteins both in the blood and in the brain structure (p>0.05) **(Fig. 5)**.

DISCUSSION

Most of the analgesics have adverse side effects, as some of them are related to general sedation and/or impairment of the attention, motivation, or memory. KTP derivatives demonstrated strong analgesic activity with the side-effects corresponding with a reduction in micturition, and a mild

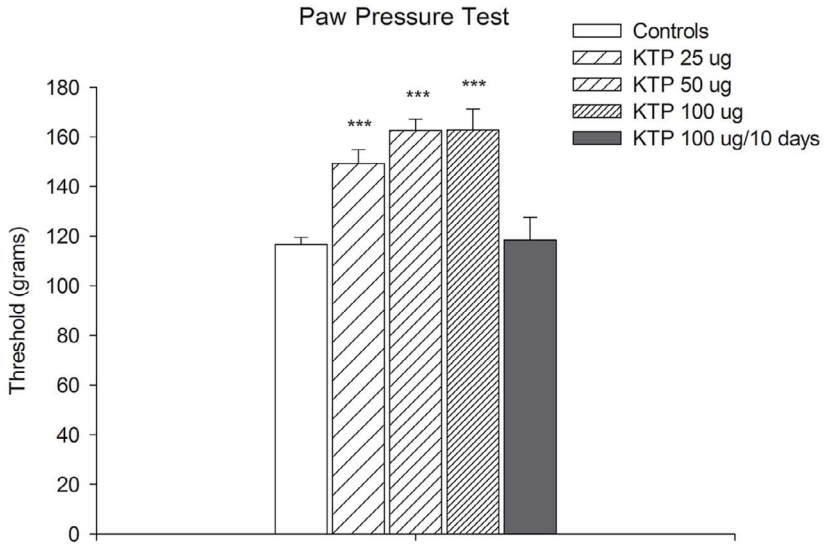

Figure 1. KTP injected ICV at doses of 25, 50 and 100 μg/rat increased pain threshold in Paw pressure test in rats as compared to the Controls injected with aCSF. The chronic KTP at a dose of 100 μg/rat for 10 days did not change significantly the pain threshold. Data presented as means ± SEM with n=10. *** p<0.001 vs. Controls.

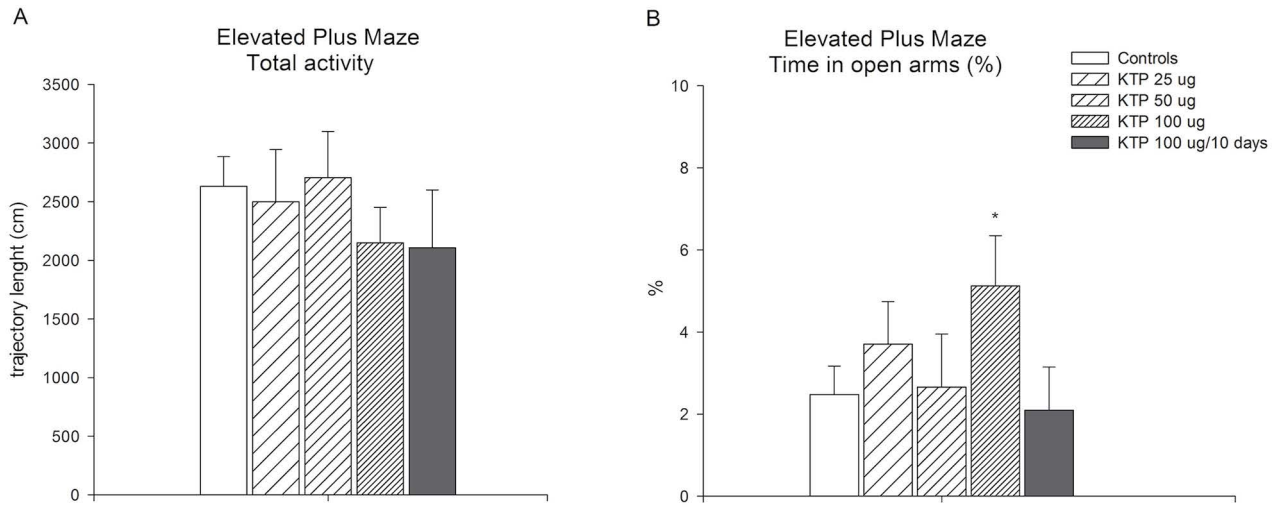

Figure 2. The total length of the trajectory (ambulation in centimetres) travelled in all zones of the Elevated plus maze (**A**), and the ratio (%) of time spent in the open arm vs. total time (5 minutes) of test (**B**) after ICV injections of aCSF (Controls) or KTP at doses of 25, 50, 100 μg/rat and 100 μg/rat for 10 days. Data presented as means ± SEM with n=10. * $p<0.05$ vs. Controls.

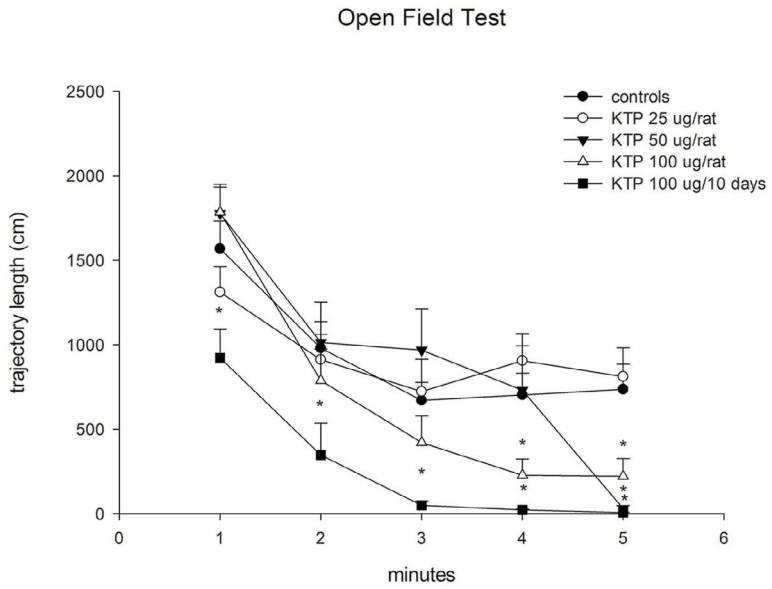

Figure 3. The total length of the trajectory (ambulation in centimetres) travelled each minute in the Open field apparatus after ICV injections of aCSF (Controls) or KTP at doses of 25, 50, 100 μg/rat and 100 μg/rat for 10 days. Data presented as means ± SEM with n=10. *$p<0.05$ vs. Controls.

motor impairment that was less deleterious than in the opioids.[14,23] The influence of the effective analgesics dose of the dipeptide on the cognitive behavior and memory processes in healthy rats, however, is still not elucidated. According to others, we showed that ICV injection of three doses of KTP exerted an antinociceptive effect.[1,5,6,8,24] The sub-chronic treatment, however, did not change the pain threshold as compared to the single doses. This result implies the occurrence of adaptation or development of a tolerance to the antinociceptive action of KTP. It is known that the development of the tolerance to opioid-induced analgesia includes not only desensitization, down-regulation, or internalization of opioid receptors, but also the anti-opioid peptides which take a part in the mechanism opioid tolerance.[25] Besides its antinociceptive properties, KTP has shown to decrease morphine-induced analgesia in hot plate test in rats, acting as an anti-opioid peptide.[26] Only a few studies provided data for the existence of an inhibitory effect of KTP on rat's attention toward various sensory stimuli and decreased motor activity. [27] The authors suggested the participation of the brain serotoninergic system in the KTP-induced modulation of these behavioral parameters. The existing data showed that KTP produces no marked changes such as hypermotility, ataxia, or cata-

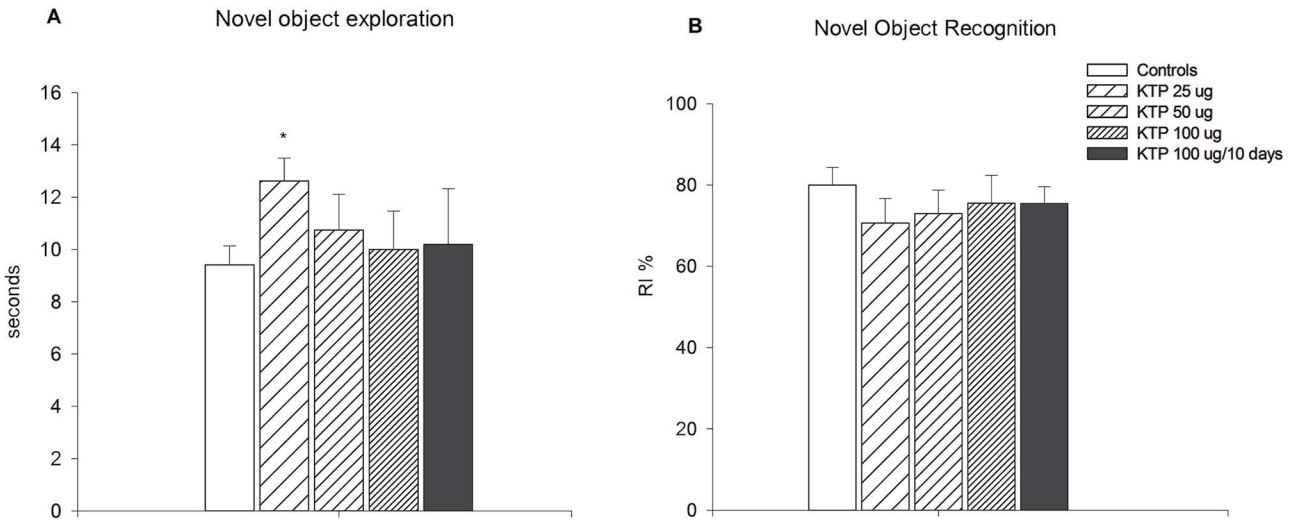

Figure 4. The total time (in seconds) spent in exploration of the new objects during the training phase of NORT (**A**), and the recognition index (%) representing the referent exploration of a new object during the test phase (**B**) after ICV injections of aCSF (Controls) or KTP at doses of 25, 50, 100 μg/rat and 100 μg/rat for 10 days. Data presented as means ± SEM with n=10. *p<0.05 vs. Controls.

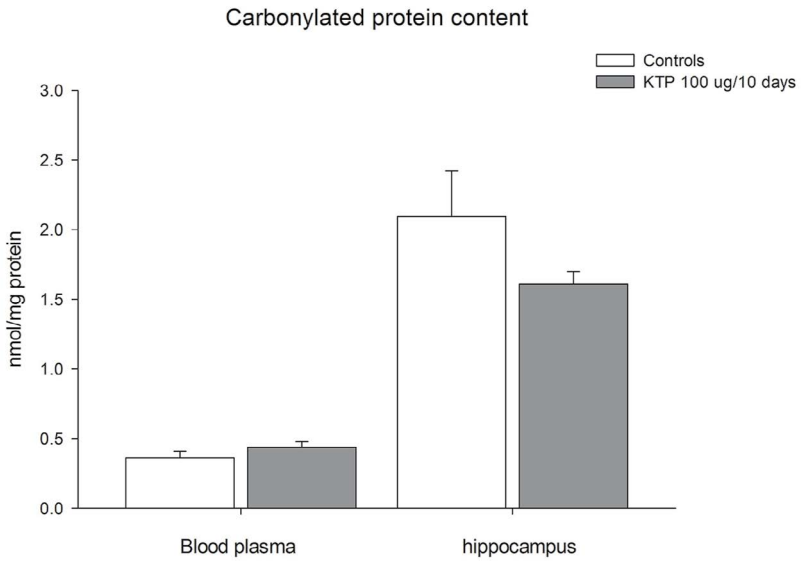

Figure 5. Total concentration of the carbonylated proteins (in mmol/mg proteins) in the blood plasma and the isolated hippocampus after ICV injections of aCSF (Controls) or KTP at a dose of 100 μg/rat for 10 days. Data presented as means ± SEM with n=10.

lepsy in rats.[27,28] Exploration is one of the basic adaptive behavior that is part of the inherent motivation, giving the animal an advantage to survive in a new or changing environment. Brain hippocampus is an analyzing neuronal circuit involved in the incentive motivated exploration, anxiety, spatial, and long-term memory.[29,30-32] Our present data from the EPM showed that only the highest single dose of KTP can suppress anxiety-like behavior. This mild sedative effect could not be explained by a KTP-induced opioid-dependent mechanism because, according to the literature, morphine treatment produced the opposite effect, but the ability of proper KTP receptor-mediated anxiolytic effect cannot be ignored.[33] We have previously shown that ICV infusion of KTP in a model of Alzheimer's disease prevented the disintegration of normal anxiety behavior in rats treated with streptozotocin.[13,16] The present results from the OFT showed a dose-dependent improvement of the habituation to a new environment of rats treated with KTP as compared to the controls. The only literature data found was related to the effects of two halogen analogs of KTP on the behavior, which demonstrated improved habituation to a new environment after two or three ICV injections in mice, while a single injection did not exert any effect on the exploration.[34] The habituation to unknown stimuli without biological significance to a subject is one of the simplest models of the learning process

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widely accepted as a form of implicit memory.[35] The ameliorative effect of KTP on the novelty habituation was not accompanied by diminished curiosity in the training phase of NORT, as far as the low dose of the dipeptide increased the time of exploration of a new object. The formation of carbonylated proteins is the most general and widely used marker of protein oxidation both in vitro and in vivo. The present study showed that neither acute injection of KTP nor its chronic administration influenced the working memory in NORT and the levels of the carbonylated proteins in blood plasma and the isolated hippocampus.

CONCLUSIONS

These results support the suggestion that the analgesic doses of KTP have no any adverse side effects on normal memory processing. We have previously shown that KTP can prevent the development of Alzheimer's type of impairment of the recognition memory when the peptide was infused chronically before and after the injection of streptozotocin.[16] The present data revealed that KTP itself has not memory-enhancing action and its action in the Alzheimer's experimental model perhaps is a result of prevention against the deleterious impact of the streptozotocin both in the early and the late phase of the development of the experimental model.[13,16] Altogether, our results showed that KTP administered directly into the brain ventricles exerted its main antinociceptive effect without affecting negatively the blood and hippocampal carbonylated proteins or basic behavioral parameters related to exploration, motivation and memory formation in healthy rats.

Acknowledgments

This study was supported by St Kliment Ohridski University of Sofia, contract No 80-10-1/2020.

Conflict of Interest

All authors declare that there are no competing interests.

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Влияние антиноцицептивного дипептида L-тирозин-L-аргинина (киоторфина) на мотивацию, тревогу и память у крыс

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Дата получения: 4 мая 2020 ♦ **Дата приемки:** 15 июня 2020 ♦ **Дата публикации:** 30 апреля 2021

Образец цитирования: Angelova H, Krumova E, Dzhambazova E, Pechlivanova D. Effects of the antinociceptive dipeptide L-tyrosine-L-arginine (kyotorphin) on the motivation, anxiety, and memory in rats. Folia Med (Plovdiv) 2021;63(2):189-96. doi: 10.3897/folmed.63.e53912.

Резюме

Введение: Эндогенный дипептид L-тирозин-L-аргинин (киоторфин, КТФ) обнаружен в структурах мозга, участвующих в обработке информации о болевых ощущениях, контроле эмоций и формировании памяти. Помимо антиноцицептивного действия КТФ, он обладает умеренной защитной активностью против вредного воздействия церебральной гипоперфузии и стрептозотоцина на поведение и память.

Цель: Наша цель состояла в том, чтобы изучить влияние интрацеребровентрикулярной инъекции эффективных антиноцицептивных доз КТФ на мотивацию, память и уровни карбонилированных белков в крови и гиппокампе у здоровых взрослых самцов крыс линии Wistar.

Материалы и методы: Мы использовали механический тест давления лапы для оценки острой ноцицепции и тест открытого поля для оценки исследований и акклиматизации к новой среде, тест с приподнятым крестообразным лабиринтом для оценки тревожного поведения и тест распознавания нового объекта для оценки рабочей память. Анализ карбонилированного белка использовали для оценки окислительного повреждения белка. Результаты были проанализированы с помощью ANOVA.

Результаты: Настоящие результаты показывают, что все разовые дозы КТФ обладают антиноцицептивным эффектом, но этот эффект не наблюдался после длительного приёма. Только самая высокая доза в 100 μg смогла вызвать анксиолитический и моторный ингибирующий эффект. Ни одна из использованных доз не оказала влияния на когнитивную память или уровень карбонилированного белка.

Заключение: Наши результаты показывают, что КТФ оказывает антиноцицептивное действие, не влияя отрицательно на карбонилированный белок крови и мозга или на основные поведенческие параметры, связанные с исследованиями, мотивацией и формированием памяти у здоровых крыс.

Ключевые слова

тревога, киоторфин, память, ноцицепция, пептиды