DOI: https://doi.org/10.17816/phbn567968
Scientific Article

Antidrug effects of GTS201 dipeptide, an imitation of the second bird BDNF, in morphine-addicted rats

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Abstract

BACKGROUND: The V.V. Zakusov Research Institute of Pharmacology developed hybrid digital sensors for the first, second, and fourth BDNF patches (GSB-214, GTSB-201, and GSB-106, respectively). When tested *in vitro*, on an oxidative stress model, in the culture of hippocampal neurons NT-22, the compound GTS201 (hexamethylenediamide bis-hexanoyl-seryl-lys), a simulator of the 2nd series of BDNF, activates the TrkB spy receptor and MAPK/Erk kinase pathway but does not affect the PI3K/Akt signature pathway and has neuroprotective activity similar to BDNF.

AIM: To study the effect of GTS-201 dipeptide on the behavior of laboratory white rats during the formation of their dependency state and morphine withdrawal syndrome.

MATERIALS AND METHODS: Morphine dependence in rats was developed due to administration of morphine in a doses escalation manner ranging from 10 to 20 mg/kg twice daily at 8-h intervals for 5 days. GTS-201 was given in 1- or 5-mg/kg doses for once in 30 minutes before morphine on the 5th day of the experiment or daily (in one of the groups) for 5 days in the morning 30 minutes before morphine administration. On the 5th day of the experiment, animals were tested for the presence of specific signs of morphine withdrawal syndrome in an "open field" for 5 minutes. Four experimental groups were formed: group 1 "morphine hr. + naloxone" ("active control" group); group 2 "morphine hr. + GTS-201 (1) + naloxone"; group 3 "morphine hr. + GTS-201 (5) + naloxone"; and group 4 "morphine hr. + GTS-201 (1 × 5) + naloxone." Designations: hr. — morphine administration within 5 days; (1) and (5) — doses of substances in mg/kg, (1 × 5) — chronic administration of the peptide for 5 days.

RESULTS: When studying the effect of GTS-201 dipeptide on behavioral, somatic, and neurological markers of animal behavior after morphine withdrawal, significant changes in the severity of individual signs of withdrawal syndrome were noted. Manifestations of diarrhea were significantly decreased in all groups of animals injected with the peptide. In animals from group 3, "morphine hr. + GTS201 (5) + naloxone showed the maximum effect: diarrhea was decreased by 71.0% ($p < 0.001$), convulsions were decreased by 83.3 % ($p < 0.05$), running was decreased by 71.4% ($p < 0.01$), and vocalization was decreased by 62.5% ($p < 0.05$). GTS-201, administered at a dose of 1 mg/kg once, eliminated the appearance of escape attempts in group 2, but the peptide at the same dose completely blocked convulsive reactions in rats in group 4. Despite significant changes in individual indicators, the total index (of morphine withdrawal syndrome for groups chronically injected with morphine) did not change statistically significantly compared with group 1 of "active control." In the control group, its value in points was 7.3 ± 0.36 (100%), whereas in groups 2–4, it ranged from 6.2 (84.9%) to 6.5 (89.0%; $p > 0.05$).

CONCLUSIONS: It is assumed that the antiaddictive dipeptide activity of GTS-201 is mediated by activation of these receptors and markers/the Erk-kinase signaling pathway, which does not exclude the involvement of opioid receptor mechanisms in the implementation of the observed behavioral phenomena.

Keywords: addiction; BDNF; GTS201; morphine; oligopeptides; withdrawal syndrome.

To cite this article:
Konstantinopolsky MA, Kolik LG, Chernyakova IV, Sazonova NM, Gudasheva TA. Antidrug effects of GTS201 dipeptide, an imitation of the second bird BDNF, in morphine-addicted rats. *Psychopharmacology and biological narcology*. 2023;14(3):185–191. DOI: https://doi.org/10.17816/phbn567968

Received: 10.07.2023 **Accepted:** 22.08.2023 **Published:** 25.09.2023

УДК 616.092
DOI: https://doi.org/10.17816/phbn567968
Научная статья

Антинаркотические эффекты дипептида ГТС-201, миметика 2-й петли BDNF, у крыс, зависимых от морфина

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Аннотация

Актуальность. В НИИ фармакологии имени В.В. Закусова были созданы дипептидные димерные миметики 1-й, 2-й и 4-й петли BDNF — ГСБ-214, ГТС-201 и ГСБ-106 соответственно. Было показано, что соединение ГТС-201 (гексаметилендиамид бис-гексаноил-серил-лизина), миметик 2-й петли BDNF, активирует специфический рецептор TrkB и MAPK/Erk-киназный путь, не влияет на сигнальный путь PI3K/Akt и обладает нейропротекторной активностью, аналогично BDNF в опытах *in vitro* на модели окислительного стресса в культуре гиппокампальных нейронов линии HT-22.

Цель — изучить влияние дипептида ГТС-201 на поведение лабораторных белых крыс в процессе формирования у них состояния зависимости и синдрома отмены морфина.

Методы. Зависимость от морфина у крыс вырабатывали введением морфина в возрастающих дозах от 10 до 20 мг/кг, 2 раза в день, с интервалом 8 ч, в течение 5 сут. ГТС-201 в дозах 1 или 5 мг/кг вводили однократно за 30 мин до морфина на 5-й день эксперимента или ежедневно (в одной из групп), в течение 5 дней утром за 30 мин до введения морфина. Тестирование животных на наличие специфических признаков синдрома отмены морфина проводили на 5-й день опыта в течение 5 мин в «открытом поле». Были сформированы 4 экспериментальные группы: группа 1 (группа активного контроля) — «морфин хр. + налоксон»; группа 2 — «морфин хр. + ГТС-201 (1) + налоксон»; группа 3 — «морфин хр. + ГТС-201 (5) + налоксон»; группа 4 — «морфин хр. + ГТС-201 (1 × 5) + налоксон» (обозначения: хр. — введение морфина в течение 5 дней; (1) и (5) — дозы веществ в мг/кг, (1 × 5) — хроническое введение пептида в течении 5 дней).

Результаты. При изучении влияния дипептида ГТС-201 на поведенческие, соматические и неврологические показатели поведения животных после отмены морфина были отмечены значимые изменения выраженности отдельных признаков синдрома отмены. Проявления диареи существенно уменьшались во всех группах животных, которым вводили пептид. У животных из группы 3 был отмечен максимальный эффект: диарея снижалась на 71,0 % ($p < 0,001$), судороги — на 83,3 % ($p < 0,05$), бегство — на 71,4 % ($p < 0,01$), вокализация — на 62,5 % ($p < 0,05$). В группе 2 ГТС-201, вводимый в дозе 1 мг/кг однократно, полностью устранял появление попыток бегства, в то время как в группе 4, при хроническом введении, пептид в той же дозе полностью блокировал судорожные реакции у крыс. Несмотря на значимые изменения отдельных показателей, суммарный индекс синдрома отмены морфина для групп, которым хронически вводили морфин, не изменялся статистически значимо в сравнении с группой 1 активного контроля. В контрольной группе его значение составило 7,3 ± 0,36 балла (100 %), тогда как в группах 2, 3, 4 — от 6,2 (84,9 %) до 6,5 (89,0 %) балла, $p > 0,05$.

Заключение. Предполагается, что обнаруженная антиаддиктивная активность дипептида ГТС-201 может быть опосредована активацией TrkB-рецепторов и MAPK/Erk-киназного сигнального пути, что не исключает участия опиоидных рецепторных механизмов в реализации отмеченных поведенческих феноменов.

Ключевые слова: олигопептиды; ГТС-201; BDNF; морфин; зависимость; синдром отмены.

Как цитировать:
Константинопольский М.А., Колик Л.Г., Чернякова И.В., Сазонова Н.М., Гудашева Т.А. Антинаркотические эффекты дипептида ГТС-201, миметика 2-й петли BDNF, у крыс, зависимых от морфина // Психофармакология и биологическая наркология. 2023. Т. 14, № 3. С. 186–191. DOI: https://doi.org/10.17816/phbn567968

Рукопись получена: 10.07.2023 **Рукопись одобрена:** 22.08.2023 **Опубликована:** 25.09.2023

ЭКО • ВЕКТОР

BACKGROUND

Previously, at the V.V. Zakusov Research Institute of Pharmacology, dipeptide dimeric mimetics of loops 1, 2, and 4 of the brain-derived neurotrophic factor (BDNF) were created, namely, bis-monosuccinyl-methionyl-serine heptamethylenediamide (GSB-214), bis-hexanoyl-seryl-lysine hexamethylenediamide (GTS-201), and bis-monosuccinyl-seryl-lysine hexamethylenediamide (GSB-106), respectively. Studies have found that GTS-201, a mimetic of BDNF loop 2, activates the specific receptor TrkB and the MAPK/Erk kinase pathway, does not affect the PI3K/Akt signaling pathway, and has neuroprotective activity similar to BDNF in *in vitro* experiments, in an oxidative stress model, and in the culture of HT-22 line hippocampal neurons [1, 2].

For the first time, this study examined the effect of the dipeptide GTS-201 on various behavioral indicators of laboratory white rats during the development of dependence and withdrawal syndrome (WS) of morphine. Data were compared with the corresponding indicators for GSB-106, one of the promising and previously studied peptide compounds, in terms of possible correction of opiate addiction [3, 4].

This study aimed to investigate the effect of GTS-201 on various behavioral indicators of laboratory white rats during the development of dependence and WS of morphine.

RESEARCH METHODS

The experiments were performed on 80 outbred male rats weighing 240–260 g. The animals were obtained from the Stolbovaya nursery. Before the start of the experiment, they were kept for 1 week in standard plastic cages, with eight rats each, in a vivarium under natural light and air temperature of 21–23°C. Granulated food and water were given *ad libitum*.

The experiments were performed in accordance with the requirements imposed in the Order of the Ministry of Health of the Russian Federation dated April 1, 2016, No. 199n "On approval of the Rules of Good Laboratory Practice" and Decisions of the Council of the European Economic Union No. 81 "On approval of the Rules of Good Laboratory Practice of the Eurasian Economic Union in the Area of Circulation of Medicines." All animal procedures were approved by the bioethical commission of the V.V. Zakusov Research Institute of Pharmacology, with the decision of the ethical committee in Protocol No. 7 of May 16, 2022.

To reduce the stress level and adapt to the experimental conditions, the animals were subjected to a handling procedure for 3–4 days before the experiment started. One day before the start of the experiment, the rats were placed in an experimental room with natural lighting changes and air temperature maintained within 23 ± 1.0°C. The animals were weighed every other day for 12 days, starting from day 1 of the administration of morphine and GTS-201. The average bodyweight changes in groups were calculated according to the number of days of the experiment.

Morphine hydrochloride was administered in doses of 10–20 mg/kg, and μ-opioid receptor agonist (Chimkent Pharmaceutical Plant), naloxone hydrochloride, an antagonist of μ-opioid receptors (DuPont DeNemours Int. S.A., Switzerland), was injected at a single dose of 1 mg/kg to provoke WS of morphine. GTS-201, hexamethylenediamide bis(N-hexanoyl-L-seryl-L-lysine), a mimetic of BDNF loop 2 (V.V. Zakusov Research Institute of Pharmacology), was administered in doses of 1 and 5 mg/kg. The substances were dissolved in distilled water and administered *extempore* intraperitoneally at a dose of 1 mL/1 kg of animal bodyweight.

Four experimental groups were formed: group 1 received chr. morphine + naloxone (active control group), group 2 received chr. morphine + GTS-201 (1) + naloxone, group 3 received chr. morphine + GTS-201 (5) + naloxone, and group 4 received chr. morphine + GTS-201 (1 × 5) + naloxone (where chr. indicated the administration of morphine for 5 days; (1) and (5) were doses of substances in mg/kg, (1 × 5) indicated chronic administration of the peptide within 5 days).

Morphine addiction was induced in rats according to a previously developed scheme, i.e., morphine was administered in increasing doses, from 10 to 20 mg/kg, two times a day, with an interval of 8 h, for 5 days [5]. GTS-201 was administered in single doses of 1 or 5 mg/kg 30 min before morphine administration on day 5 of the experiment or daily in one of the groups for 5 days in the morning 30 min before morphine administration. The animals were assessed for the presence of specific signs of morphine WS on experiment day 5 for 5 min in an "open field" (lit round arena) 15 min after the administration of the opiate receptor antagonist naloxone. The control group received daily injections of distilled water for 5 days according to the same regimen as animals from the experimental groups; they received naloxone at a dose of 1 mg/kg on day 5 of the experiment, before testing. Behavioral reactions, namely, locomotor activity, stances, grooming, defecation, and specific signs of morphine WS (up to 18 indicators), were registered in all groups. Discrete signs of withdrawal (such as diarrhea and episodes of shaking and grinding of teeth) were assessed quantitatively and alternatively, and the rest were evaluated in an alternative form, according to the "yes/no" principle. The total index (TI) of WS severity for each animal and the average values for the experimental and control groups were calculated based on alternative signs with the maximum possible TI value of 18 points. The average value of the WS severity in group 1 was 100%.

To assess the effect of GTS-201 on the behavior of morphine-dependent rats in the elevated plus maze (EPM) test, a standard configuration was used, with an arm length of 50 cm, width of 14 cm, central platform of 14 × 14 cm, and height of sides of closed arms of 15 cm. At 24 h after the withdrawal of morphine injections, standard behavioral

indicators were recorded for 5 min, namely, the number of entries into the open arms, time spent in the open arms in seconds, and number of entries into the closed arms.

Tactile thresholds were assessed in rats using the von Frey test using a standard set of filaments from Ugo Basile (Italy), which can exert graded pressures on the plantar surface of the hind paws of rats. Each measurement with a separate filament was performed at least three times, the animals' response to pressure was assessed, and strength was presented in grams. For each group, tactile thresholds were measured at baseline, before the use of substances, and 24 h after morphine withdrawal and last administration of the GTS-201 dipeptide.

Statistical analysis was performed using the analysis of variance (ANOVA) test, Mann–Whitney *U*-test, and Duncan test to compare differences between the groups. Data were presented as mean values ± error of the mean (*m* ± *SEM*), as well as percentage relative to the initial level of values in each test. Data with p values < 0.05 were assessed as statistically significant.

RESEARCH RESULTS AND DISCUSSION

Changes in animal bodyweights were recorded by groups for 12 days. Statistically significant changes in this indicator were noted from day 5, from the start of morphine administration. In groups 1 and 2 by this day, the average decrease in bodyweight was 11% ($p < 0.05$) from the initial level. After morphine withdrawal, on day 7 of the experiment, the maximum decreases in bodyweights in groups 1, 2, and 3 were 17.8%, 16.9%, and 14.6%, respectively ($p < 0.01$). When administered chronically, GTS-201 blocked a decrease in bodyweight in morphine-dependent rats in group 4 (Table 1).

Tactile thresholds in rats were markedly reduced in all groups after morphine withdrawal. However, after the administration of GTS-201, a partial restoration of tactile

Table 1. Weight changes of rat body after administration of morphine and GTS-201 compound (*m* ± S.E.M.)
Таблица 1. Изменение массы тела крыс под влиянием морфина и соединения ГТС-201 (*m* ± S.E.M.)

Days of experiment	Bodyweight of rats (g) in the experimental groups							
	Group 1		Group 2		Group 3		Group 4	
	gram	%	gram	%	gram	%	gram	%
1	273.5 ± 4.9	100	282.5 ± 2.5	100	272.0 ± 4.6	100	283.0 ± 3.3	100
3	260.5 ± 6.2	95.2 ± 1.4	271.5 ± 3.6	96.1 ± 1.4	261.5 ± 3.9	96.2 ± 1.4	272.5 ± 5.6	96.2 ± 1.2
5	243.5 ± 5.2	89.0* ± 0.6	251.5 ± 2.1	89.0* ± 0.5	254.5 ± 4.6	93.5 ± 0.9	261.0 ± 6.7	92.1 ± 1.7
7	224.8 ± 4.3	82.2** ± 1.1	234.7 ± 2.3	83.1** ± 0.9	232.3 ± 3.8	85.4** ± 1.2	264.6 ± 4.6	93.5# ± 1.5
12	266.4 ± 4.8	97.4 ± 1.3	273.2 ± 1.8	96.7 ± 0.8	263.8 ± 4.2	97.0 ± 0.9	277.9 ± 3.9	98.2 ± 1.3

Note. *$P < 0.05$; **$P < 0.01$ when comparing bodyweight values on days 5 and 7 with values on day 1 of the experiment. #$P < 0.05$ when comparing groups 1 and 4 on day 7 of the experiment. The groups are described in the Methods section.
Примечание. *$P < 0,05$; **$P < 0,01$ при сравнении величин массы тела в 5-й и 7-й дни с значениями в 1-й день эксперимента. #$P < 0,05$ при сравнении гр. 1 и гр. 4 в 7-й день эксперимента. Описание групп см. в разделе «Методы исследования».

Table 2. Tactil thresholds changes in morphine-depended rats in von Frey's test (*m* ± S.E.M.)
Таблица 2. Изменения тактильных порогов у морфин-зависимых крыс в тесте von Frey (*m* ± S.E.M.)

Experimental groups	Baseline values		After withdrawal	
	Gram	%	Gram	%
Group 1	0.72 ± 0.06	100	0.05 ± 0.005 $P = 0.004^{\#\#}$	7.67 ± 0.93
Group 2	0.82 ± 0.09	100	0.18 ± 0.04 $P = 0.02^{\#}$	25.56 ± 7.04 $P = 0.02$*
Group 3	0.88 ± 0.06	100	0.17 ± 0.03 $P = 0.02^{\#}$	20.10 ± 2.70 $P = 0.004$**
Group 4	1.02 ± 0.14	100	0.13 ± 0.03 $P = 0.01^{\#\#}$	12.47 ± 1.98 $P = 0.04$*

Notes. #$P < 0.05$; ##$P < 0.01$ between the initial values of tactile thresholds and their values after morphine withdrawal; *$P < 0.05$; **$P < 0.01$ between the values of tactile thresholds for group 1 in comparison with the morphine-dependent groups receiving GTS-201. The ANOVA test, Mann–Whitney *U*-test, and Duncan test were used to compare between-group differences.
Примечания. #$P < 0,05$; ##$P < 0,01$ между исходными величинами тактильных порогов и их значениями после отмены морфина; *$P < 0,05$; **$P < 0,01$ между величинами тактильных порогов для группы 1 в сравнении с группами морфин-зависимых животных, получавших дипептид ГТС-201. Тест ANOVA, Mann–Whitney *U*-test и Duncan test для сравнения различий между группами.

DOI: https://doi.org/10.17816/phbn567968

thresholds was note, most pronounced for group 2 at 25.6% ($p < 0.05$) and group 3 at 20.1% ($p < 0.01$) and to a lesser extent for group 4 at 12.5% ($p < 0.05$) of the initial values. These values were statistically significantly different from the average threshold values in group 1 (control) (Table 2).

When studying the effect of GTS-201 on the behavior of morphine-dependent rats in the EPM test, no significant differences in the number of entries into open arms and the time spent in them were noted between active control group 1 and group 2. A moderately pronounced tendency was noted toward a decrease in these indicators when comparing groups 1 and 3 ($p = 0.1$) (Table 3).

When studying the effect of GTS-201 on behavioral, somatic, and neurological indicators of animal behavior after morphine withdrawal, significant changes in the pronouncement of individual signs of WS were noted. The incidence of diarrhea decreased significantly in all groups that received the peptide. In group 3, the maximum effect was noted, that is, diarrhea decreased by 71.0% ($p < 0.001$), convulsions by 83.3% ($p < 0.05$), escape attempts by 71.4% ($p < 0.01$), and vocalization by 62.5% ($p < 0.05$). In group 2, GTS-201, which was administered at a single dose of 1 mg/kg, eliminated completely escape attempts, whereas in group 4, the same dose of peptide administered chronically arrested completely convulsive reactions in rats. Despite significant changes in individual parameters, the TI of morphine WS for the groups that received morphine chronically did not change statistically significantly compared with that in the active control group, with values of 7.3 ± 0.36 points (100%) in the control group and 6.2–6.5 points (84.9%–89.0%) in groups 2, 3, and 4 ($p > 0.05$; Table 4).

CONCLUSION

The ability of GTS-201, a bis(-N-hexanoyl-L-seryl-L-lysine) hexamethylenediamide, a BDNF loop 2 mimetic, to

Table 3. Effect of dipeptide GTS-201 on behavior of morphine-depended rats in elevated plus maze test (m ± S.E.M.)

Таблица 3. Влияние дипептида ГТС-201 на поведение зависимых от морфина крыс в тесте приподнятого крестообразного лабиринта (m ± S.E.M.)

Groups of animals	Entries into open arms	Time spent in open arms (s)	Entries into closed arms
Group 1	2.4±0.74	25.2±7.20	4.3±0.96
Group 2	2.0±0.39 $P = 0.58^{*}$	27.6±5.90 $P = 0.77^{*}$	3.7±0.75 $P = 0.58$
Group 3	1.1±0.27 $P = 0.10^{*}$; $0.22^{\#}$	11.6±3.37 $P = 0.10^{*}$; $0.14^{\#}$	3.5±0.54 $P = 0.50^{*}$; $0.85^{\#}$

Note. Statistical differences between and within each group were not significant.
Примечание. Статистические различия между и внутри каждой группы не были значимы.

Table 4. Effect of dipeptide GTS-201 on behavior indexes of withdrawal syndrome of morphine in rats (m ± S.E.M.)

Таблица 4. Влияние дипептида ГТС-201 на поведенческие показатели синдрома отмены морфина у крыс (m ± S.E.M.)

Behavioral traits	Experimental groups			
	Group 1	Group 2	Group 3	Group 4
Morphine WS index	7.3±0.36	6.5±0.36 $P = 0.45$ n.s.	6.2±0.48 $P = 0.48$ n.s.	6.4±0.47 $P = 0.19$ n.s.
Diarrhea	3.1±0.27	$2.1±0.36^{*}$	$0.9±0.48^{***}$	$1.6±0.47^{**}$
Posture	0.5±0.16	0.9±0.18	0.8±0.13	0.8±0.13
Ptosis	0.7±0.12	0.6±0.14	0.8±0.13	0.3±0.12
Piloerection	0.8±0.13	0.7±0.16	0.9±0.16	0.8±0.13
Rhinorrhea	0.4±0.10	0.0±0.0	0.4±0.12	0.7±0.14
Dyspnea	0.8±0.13	0.9±0.16	0.9±0.16	0.9±0.16
Writhing	0.4±0.12	0.3±0.12	0.2±0.12	0.1±0.11
Convulsions	0.6±0.16	0.3±0.11	$0.1±0.11^{*}$	$0.0±0.0^{**}$
Escape attempts	0.7±0.16	$0.0±0.0^{**}$	$0.2±0.12^{**}$	0.7±0.14
Вокализация	0.8±0.13	0.8±0.14	$0.3±0.14^{*}$	0.6±0.12

Notes. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ between the values of behavioral indicators for group 1 in comparison with those for the morphine-dependent group receiving GTS-201. ANOVA test, Mann–Whitney *U*-test, and Duncan test were used to compare between-group differences. WS, withdrawal syndrome; n.s., not significant.
Примечание. $^{*}P < 0{,}05$; $^{**}P < 0{,}01$; $^{***}P < 0{,}001$ между величинами поведенческих показателей для группы 1 в сравнении с этими показателями для групп морфин-зависимых животных, получавших дипептид ГТС-201. Тест ANOVA, Mann–Whitney *U*-test и Duncan test для сравнения различий между группами. СО — синдром отмены; н.д. — не достоверны.

influence somatic, behavioral, and neurological signs of morphine dependence was examined using laboratory rats. In the EPM test, GTS-201, which was administered at a dose of 5 mg/kg, showed a moderate tendency ($p = 0.1$) to reduce the number of entries and time spent in the open arms of the maze. The ability of GTS-201 to eliminate or reduce the incidence of certain manifestations of morphine WS in rats, such as diarrhea, vocalization, attempts to escape, and convulsions, has been demonstrated. The single-dose peptide in doses of 1 or 5 mg/kg restored partially the level of tactile threshold in rats, which was reduced after morphine withdrawal. GTS-201, which was administered chronically to animals at a dose of 1.0 mg/kg, restored bodyweight decreases caused by morphine withdrawal. Despite the changes in individual indicators, the TI of morphine WS for different experimental groups did not differ statistically significantly when compared with that of the active control group. A comparison of the results obtained from studying GTS-201 with the corresponding previously presented data for GSB-106, the BDNF loop 4 mimetic, showed a noticeable advantage of the latter in reducing the incidence of behavioral manifestations of morphine WS in rats. Thus, the detected anti-addictive activity of GTS-201 may be mediated by the activation of TrkB receptors and the MAPK/Erk kinase signaling pathway, which does not exclude the participation of opioid receptor mechanisms in the implementation of the registered behavioral phenomena.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. The contribution of each author: M.A. Konstantinopolsky, L.G. Kolik, I.V. Chernyakova, N.M. Sazonova — manuscript drafting, writing and pilot data analyses; T.A. Gudasheva — general concept discussion.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Вклад каждого автора: М.А. Константинопольский, Л.Г. Колик, И.В. Чернякова, Н.М. Сазонова — написание статьи, анализ данных; Т.А. Гудашева — разработка общей концепции.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

REFERENCES

1. Logvinov IO, Tarasiuk AV, Sazonova NM, et al. Comparison of neuroprotective properties of the dipeptide mimetics of the 1st, 2nd and 4th loops of the brain-derived neurotrophic factor on the model oxidative stress ***in vitro***. *Pharmacokinetics and Pharmacodynamics*. 2018;(3):37–41. (In Russ.) DOI: 10.24411/2587-7836-2018-10022

2. Logvinov IO, Tarasyuk AV, Kruglov SV, et al. Dipeptidnyi mimetik mozgovogo neirotroficheskogo faktora GTS-201 obladaet neiroprotektornoi aktivnost'yu i selektivno aktiviruet MAPK/ERK signal'nyi put'. *Ekperimental'naya i klinicheskaya farmakologiya*. 2018;81:145–146. (In Russ.) DOI: 10.30906/0869-2092-2018-81-5s-145-146

3. Konstantinopolsky MA, Gudasheva TA, Kolik LG. The BDNF mimetic, GSB-106, produces long-term analgesia and significant reduction of opiate withdrawal signs: comparison with dipeptide anxiolytic GB-115 effects in rats. *Eur Neuropsychopharmacol*. 2016;26(Suppl 2):S680–S681.

4. Konstantinopolsky MA, Gudasheva TA, Kolik LG. New types of activity of the BDNF dipeptide mimetic: A psychostimulant, anti-opioid and anti-craving effects in opiate dependent rodents. *Eur Neuropsychopharmacol*. 2019;29(Suppl 6). DOI: 10.1016/j.euroneuro.2019.09.782

5. Konstantinopol'skii MA, Chernyakova IV. Afobazol snizhaet vyrazhennost' sindroma otmeny morfina v eksperimente. *Ekperimental'naya i klinicheskaya farmakologiya*. 2011;74(10):12–16. (In Russ.) DOI: 10.30906/0869-2092-2011-74-10-12-16

СПИСОК ЛИТЕРАТУРЫ

1. Логвинов И.О., Тарасюк А.В., Сазонова Н.М., и др. Сравнение нейропротекторных свойств дипептидных миметиков 1-й, 2-й и 4-й петель мозгового нейротрофического фактора на модели окислительного стресса in vitro // Фармакокинетика и фармакодинамика. 2018. Т. 3. С. 37–41. DOI: 10.24411/2587-7836-2018-10022

2. Логвинов И.О., Тарасюк А.В., Круглов С.В., и др. Дипептидный миметик мозгового нейротрофического фактора ГТС-201 обладает нейропротекторной активностью и селективно активирует MAPK/ERK сигнальный путь // Экпериментальная и клиническая фармакология. 2018. Т. 81. С. 145–146. DOI: 10.30906/0869-2092-2018-81-5s-145-146

3. Konstantinopolsky M.A., Gudasheva T.A., Kolik L.G. The BDNF mimetic, GSB-106, produces long-term analgesia and significant reduction of opiate withdrawal signs: comparison with dipeptide anxiolytic GB-115 effects in rats // Eur. Neuropsychopharmacol. 2016. Vol. 26. Suppl. 2. P. S680–S681.

4. Konstantinopolsky M.A., Gudasheva T.A., Kolik L.G. New types of activity of the BDNF dipeptide mimetic: a psychostimulant, anti-opioid and anti-craving effects in opiate dependent rodents // Eur. Neuropsychopharmacol. 2019. Vol. 29. Suppl. 6. DOI: 10.1016/j.euroneuro.2019.09.782

5. Константинопольский М.А., Чернякова И.В. Афобазол снижает выраженность синдрома отмены морфина в эксперименте // Экспериментальная и клиническая фармакология. 2011. Т. 74. № 10. С. 12–16. DOI: 10.30906/0869-2092-2011-74-10-12-16

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