Journal of Bioterrorism & Biodefense

Severyanova and Plotnikov, J Bioterror Biodef 2018, 9:1
DOI: 10.4172/2157-2526.1000160

Research Article Open Access

Influence of Various Compounds with Glyprolines on Acth-4-7 Effects in Pain-Induced Aggressive-Defensive Behavior in Rats

Severyanova LA[1]* and Plotnikov DV[2]

[1]Department of Pathophysiology, Kursk State Medical University, Kursk, Russia
[2]Psychiatry Department, Kursk State Medical University, Kursk, Russia

Abstract

We studied the effects of $ACTH_{4-7}$ (the N-terminal fragment of the corresponding pituitary hormone molecule) on the pain-induced aggressive-defensive behavior in the foot-shock model in rats. The peptide was administered intraperitoneally in the saline at the doses 17, 50, 150 and 450 mcg/kg 12 min before the unavoidable painful stimulation of a pair of rats in an electrified camera. The analgesic and anti-aggressogenic effects of the peptide were found. These effects were significally enhanced after administration of the peptides synthesized by means of binding of the amino acids chain Pro-Gly-Pro to one or both ends of $ACTH_{4-7}$ molecule. The data obtained increase the possibility of searching and using drugs to correct aggression.

Keywords: Regulatory peptides; $ACTH_{4-7}$; Glyprolines; Pain; Aggression

Introduction

According to modern concept, aggression is very important for survival and an universal form of behavior because it is inherent in various species and is mostly diverse in origin and nature. In humans aggression has many social manifestations beginning from a failure in activity Savage, et al. [1] as well as the clinical cases such as traumatic brain damage [2]. But, the pain-induced aggressive behavior should be considered as the most common and very often found in human's form of aggression, so to study the mechanisms of its development and correction is a really urgent medical and social problem. The brain peptides were revealed (arginine-vasopressin, oxytocin, opioid and other peptides) which influence the nociceptive and antinociceptive structures at the same time involved in the formation of aggression [3]. It is of particular interest to study the effects of the adrenocorticotropic hormone (ACTH) of the pituitary gland on the pain and aggression since its release is increased in any stress condition [4]. The peptide $ACTH_{4-7}$ an N-terminal fragment of the corresponding hormone is the object of the study since it possesses not endocrinotropic,but neurotropic activity [4]. To increase the resistance to the action of peptidases the tripeptide glyproline Pro-Gly-Pro, (PGP) consisting of the residues of amino acids proline (P) and glycine (G) was added to the C-terminus of $ACTH_{4-7}$ and the peptide was called "Semax" [5,6]. A review of numerous studies has shown the multiple drug effects: on the memory, attention, and training and on other brain functions [7]. To date, various glyprolines have been synthesized, forming a new group of peptide regulators. The neurotropic effects of the peptide PGP-$ACTH_{4-7}$- PGP are to be studied. This is relevant since the glyprolines not only stabilize the peptides, but also promote the appearance of new properties [6].

The purpose of our study is to reveal the peculiarities of the influence of the oligopeptides $ACTH_{4-7}$, $ACTH_{4-7}$-PGP (Semax) and PGP-$ACTH_{4-7}$- PGP on the pain-induced aggressive-defensive behavior in rats.

Materials and Methods

The study was performed on 140 male Wistar rats, weighing 180-200 g, obtained from the "Stolbovaya" nursery of the Russian Academy of Sciences. The animals were kept under standard conditions: free access to water and food, a 12-hour lighting regimen and at temperature of 22 ± 2°C. A model of unavoidable stimulation of a pair of rats in a chamber with an electrified grid floor was used, to which an alternating current was applied gradually (1 V per 1 s) [8]. The values of the thresholds of the reactions of flinching, vocalization, rising, running and fighting were recorded, as well as the number of attacks (% of the number of trials) in a group of 10 rats. The test was repeated at 1 minute intervals. Each time it was stopped when fighting reactions occurred or when 70 V was reached. The peptides were administered intraperitoneally in a physiological saline at doses of 17.0; 50.0; 150.0 or 450 μg/kg 12 minutes. Before the test, animals of the control group-an equivalent volume of the solvent (1ml/kg). The tests were conducted from 9 a.m. till 1 p.m. The peptides were synthesized at the Institute of Molecular Genetics of the Russian Academy of Sciences. The significance of differences was determined by Students T-test. During carrying out the work, we were guided by the requirements of the international agreements on humane treatment of animals (The European Communities Council Directives of 24 November 1986-806609 EEC) and the decision of the Regional Ethics Committee.

Results

In response to the gradually increased unavoidable irritation of the paired animals the pain arises the intensification of which is accompanied by the appearance of fear which also increases and results in the arising of attacks as an outbreak of aggression directed at the partner [9]. This consummatory response allows estimating the painful and affective reactions to it, resulting in the aggressive behavior.

***Corresponding author:** Severyanova LA, Professor, Department of Pathophysiology, Kursk State Medical University, Kursk, Russia, Tel: 9038711190; E-mail: severlud@yandex.ru

Received December 22, 2017; **Accepted** January 25, 2018; **Published** February 10, 2018

Citation: Severyanova LA, Plotnikov DV (2018) Influence of Various Compounds with Glyprolines on Acth-4-7 Effects in Pain-Induced Aggressive-Defensive Behavior in Rats. J Bioterror Biodef 9: 160. doi: 10.4172/2157-2526.10001609

It is also called the affective aggression. The results obtained in the study of each peptide are presented in Table 1. The average values of the thresholds of the behavioral components developed during the gradual increase in the stimulus strength were generated: flinching and vocalization (estimated as indicators of pain sensitivity), rising up and running (indicators of fear), fighting (aggressiveness) and the frequency of attacks. As it can be seen from the table, the predominant change in comparison with the control values after the administration of the tetrapeptide $ACTH_{4-7}$ was an increase in the thresholds of behavioral responses. For painful responses it was the most pronounced (by 23-34%) and reached a level of statistical significance (at $p<0.05$-0.001). There was also a decrease in the frequency of attacks when the peptide was administered at all doses, in addition to the dose of 50.0 μg/kg. The same increasing tendency of the thresholds of all the components of the pain-induced behavior was observed even after the administration of the peptide $ACTH_{4-7}$-Pro-Gly-Pro, especially at a dose of 50.0 μg/kg (the data of this fragment were obtained together with A.A. Kryukov). A more constant effect was a decrease in pain sensitivity and reaction of fear. As for the reaction of the fighting, its frequency did not change under the action of the peptide, and after using it at a dose of 450 μg/kg even slightly increased (by 8%). A similar tendency to weakening the reactions of pain and fear with unavoidable pain stimulation was also found after the administration of a peptide with two chains of Pro-Gly-Pro to rats. The most significant as compared to the control parameters were the analgesic and anxiolytic effects of the peptide when administered at doses of 150 and 450 μg/kg (for $p<0.001$). The same antiaggressogenic effect manifested itself in a statistically significant increase in the thresholds of the battles occurrence ($p<0.001$) with increasing doses, but the frequency of battles, practically, remained at the level of the control group.

Discussion

The data obtained by us showed that the peptide $ACTH_{4-7}$ had the analgesic and anti-aggressogenic effects. The addition of a chain PGP to the C-terminus, and especially to the C- and N-termini., leads to the intensification of the analgesic effect, a weakening of fear and aggression in unavoidable pain stimulation. As for the mechanisms of their influence it can be caused either by the direct action on the brain cells or indirectly by means the activity of the neurotransmitters systems. Thus, it is known that the melanocortin receptors 2 with which ACTH interacts ,are widely present in the brain structures that can partially mediates its neurotropic effects [4]. It was also found that glyprolines have ligand-receptor activity and specific binding sites on the plasma membranes of brain cells [6]. On the other hand, the possibility of penetration of short peptides into the cell nucleus and epigenetic regulation of gene expression was experimentally revealed [10]. The genome-wide analysis demonstrated the influence of PGP on the transcriptome of ischemic brain cortex in rats [5]. As for the peptide interactions with the brain neurotransmitter systems it was detected in a number of studies. The competition of glyprolines for the sites of a specific binding to the membranes of the basal forebrain nuclei was found for the agonists and antagonists of the cannabinoud, nicotinic and NMDA receptors [6]. The ability of $ACTH4_{-7}$ –PGP to potentiate the currents of AMPA receptors, widely represented in the hippocampus, amygdala and cortical zones was established. Beside of this the peptide neurotrophic factors control the development of neurotransmitters systems [11]. On the whole, the serotonin and other neurotransmitters are involved in the development of an aggression [12].

Conclusion

On the model of affective aggressiveness induced by pain, we have established that the analgesic and antiaggressogenic effects of the $ACTH_{4-7}$ peptide are significantly enhanced by the addition of glyproline, especially to both the C- and N-termini of the peptide molecule. These data expand the possibilities of searching and using drugs to correct pain and aggression.

Groups / Reactions	Control	17,0 (mcg)	50.0 (mcg)	150.0 (mcg)	450.0 (mcg)
АКТГ$_{4-7}$					
Flinching	21,8±0,9	29,2±1,2***	26,8±1,0*	26,8±1,7*	27,0±0,7*
Vocalization	27,9±1,2	32,9±1,5*	32,5±1,2*	30,9±1,7	29,2±0,9
Rising up	30,8±1,6	32,6±0,9	27,4±1,5	32,3±1,4	29,5±0,6
Running	33,5±1,2	32,7±0,6	32,0±1,4	34,3±1,1	33,0±1,0
Fighting	40,0±1,0	44,4±1,1**	44,4±1,2*	40,6±0,8	46,0±0,9***
Frequency of fightings	60	50	80	40	50
АКТГ$_{4-7}$ - PGP					
Flinching	30,5±1,1	30,0±1,5	35,8±1,4*	30,4±1,4	31,9±1,1
Vocalization	37,3±1,2	38,4±1,5	44,6±1,5*	37,8±1,3	41,3±1,2*
Rising up	42,6±1,3	42,4±1,5	48,6±1,4*	43,4±1,2	48,5±2,2*
Running	52,5±1,1	55,0±1,6	58,8±1,4*	53,5±1,9	56,2±1,4*
Fighting	59,8±2,7	65,3±1,3	68,4±0,4*	62,2±3,2	65,1±1,6
Frequency of fightings	50	50	42	50	58
PGP - АКТГ$_{4-7}$ - PGP					
Flinching	21,8±0,9	19,0±0,7	20,7±0,5	22,9±1,3	24,0±0,6
Vocalization	27,9±1,2	25,9±1,2	27,2±1,2	42,9±1,2	33,8±1,2***
Rising up	30,8±1,6	27,1±0,9	27,7±1,3	34,5±0,7	45,5±0,8***
Running	33,5±1,2	35,8±0,5	37,5±1,0	34,7±0,6	58,9±1,5***
Fighting	40,0±1,0	42,0±0,8	51,2±0,7***	50,4±0,5***	55,2±1,5***
Frequency of fightings	60	60	60	80	60

Note: significance of the differences is given by * – p<0,05; ** – p<0,01; *** – p<0,001.

Table 1: The thresholds values of aggressive-defensive behavior (V. M ± m) and fighting rate (in % of number of trials in a group) after administration of a corresponding peptide in rats.

References

1. Savage J, Ferguson C, Flores L (2017) The effect of academic achievement on aggression and violent behavior: a meta-analysis. Aggress Violent Behav 37: 91-101.
2. Buckley L, Kaye SA, Stork RP, Heinze JE, Eckner JT (2017) Traumatic brain injury and aggression: A systematic review and future directions using community samples. Aggress Violent Behav 37: 26-34.
3. Takahashi A, Miczek KA (2014) Neurogenetics of aggressive behavior: studies in rodents. Curr Top Behav Neurosci 17: 3-44.
4. Ghaddhab C, Vuissoz JM, Deladoev J (2017) From bioinactive ACTH to ACTH antagonist: The clinical perspective. Front Endocrinol 8: 17.
5. Medvedeva EV, Dmitrieva VG, Povarova OV, Limbroska SA, Scvortsova VI, et al. (2014) Effect of tripeptide Pro-Gly-Pro on rat brain transcriptome in focal ishemia. Mol Biol (Mosk) 48: 277-287.
6. Vyunova TV, Andreeva LA, Shevchenko KV, Shevchenko VP, Myasoedov NF (2016) The synthesis and study of simple glyprolines. Neurochemical J 10: 219-225.
7. Grigoriev VV, Andreeva LA, Zamoysky VL, Shevchenko VP, Bachurin SO, et al. (2015) The action of the peptide drug Semax on the currents of AMPA receptors of rat cerebellar Purkinje cells. Dokl Biochem Biophys 460: 47-48.
8. Rodgers RJ, Semple JM (1978) Pituitary-adrenocortical axis and shock-induced fighting in rats. Physiol Behav 20: 533-537.
9. Ilyasov FN (2017) On the relationship between aggression and fear. Social Research 1: 62-69.
10. Ashapkin VV, Linkova NS, Havinson VN, Vanyuscin BF (2015) Epigenetic mechanisms of peptidergic regulation of gene expression during aging of human cells. Biochemistry (Mosc) 80: 374-388.
11. Popova NR, Ilchibaeva TV, Naumenko VS (2017) Neurotrophic factors (BDNF, GDNF) and serotoninergic system of the brain. Biochemistry 82: 449-459.
12. Butkevich IP, Mikhaylenko VA (2016) Damaging effects at early age change pain sensitivity in adult female rats, buspirone correction. Ross fiziol zh I M Sechenov 102: 1146-1155.