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TRANSMITTER-MEDIATED ACTION OF NEUROMEDIN S ON PASSIVE AVOIDANCE LEARNING IN RATS

SIÇANLARDA TRANSMİTER ARACILI NÖROMEDİN S'İN PASİF KAÇINMA ÖĞRENME ETKİSİ

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Abstract

The possible involvement of different neurotransmitters in the action of neuromedin S (NMS) in the memory consolidation of passive avoidance behavior was studied by pretreating rats with different receptor blockers which alone did not change the test. The involvement of cholinergic, dopaminergic, adrenergic, serotonergic, opiate and GABA-ergic receptors and nitric oxide was tested. The animals were pretreated with the non selective muscarinic acetylcholine receptor antagonist, atropine, the non selective β-adrenergic receptor antagonist phenoxybenzamine, the β-adrenergic receptor antagonist propranolol, the D2, D3, D4 dopamine receptor antagonist haloperidol , the non selective 5-HT2 serotonergic receptor antagonist cyproheptadine, the nonselective opioid receptor antagonist naloxone,. the γ-aminobutyric acid subunit A (GABA-A) receptor antagonist bicuculline, or the nitric oxide synthase inhibitor nitro-L-arginine. Atropine, haloperidol, phenoxybenzamine, propranolol, cyproheptadine, naloxone and nitro-L-arginine prevented the effects of NMS on passive avoidance learning. Bicuculline did not change the effects of NMS.

The results demonstrate that muscarinic acetylcholine, α- and β- adrenergic, dopaminergic , 5-HT2 serotonergic and opioid receptors and nitric oxide are involved as mediators. In the action of NMS on the consolidation of passive avoidance learning.

Keywords: Neuromedin S passive avoidance learning, transmitters

Özet

Tek başına testi değiştirmeyen farklı reseptör blokerleri ile önceden muamele edilmiş sıçanlarla, pasif kaçınma davranışının bellek konsolidasyonunda yer alan nöromedin S (NMS) aksiyonuna farklı nörotransmiterlerin olası katılımları çalışılmıştır. Kolinerjik, Dopaminerjik, Adrenerjik, Serotonerjik, Opiat ve GABA-erjik reseptörlerin ve nitrik oksit katılımı test edilmiştir. Hayvanlara önceden non- selektif muskarinik asetilkolin reseptörü antagonisti atropin, non-selektif α-adrenerjic reseptör antagonisti fenoksibenzamin, β-adrenerjic reseptör antagonisti propranolol, D2, D3, D4 dopamin reseptör antagonisti haloperidol, non-selektif 5HT2 serotonerjik reseptör antagonisti siproheptadin, nonselektif opioid reseptör antagonisti nalokson, γ-aminobütirik asit altbirimi A (GABA-A) reseptör antagonisti bikukulin veya nitrik oksit sentez inhibitörü nitro-L-arjinin ile muamele edilmiştir. Atropin, haloperidol, fenoksibenzamin, propanolol, siproheptadin, nalokson ve nitro-L-arjinin, NMS'nin pasif kaçınmalı öğrenme üzerindeki etkilerini önlemiştir. Bikukulin NMS'nin etkilerini değiştirmemiştir. Sonuçlar muskarinik asetilkolinin, α- ve β- adrenerjik, dopaminerjik, 5-HT2 serotonerjik ve opioid reseptörlerin ve nitrik oksitin pasif kaçınmalı öğrenmenin konsolidasyonunda NMS aksiyonuna mediyatör olarak katıldığını göstermiştir.

Anahtar Kelimeler: Nöromedin S, pasif kaçınmalı öğrenme, transmiterler

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1. Introduction

Neuromedin S (NMS) is a new member of the neuromedin peptide family (Mori et al., 2005),. is highly expressed in the suprachiasmatic nucleus of the hypothalamus. Although NMS shares its C-terminal structure with neuromedin U (NMU), the N-terminal portion has no sequence homology to other known peptides, and these two neuromedins are coded by two different genes (Mori et al., 2005). NMU and NMS have been demonstrated to share their receptors, FM-3/GPR66 and FM-4/TGR-1. On the other hand, while they exhibit similar affinities for FM-3/GPR66, which may be responsible for the similarities in their effects, NMS binds with higher affinity to FM-4/TGR-1 (Mori et al., 2005), the receptor which may mediate the genuine physiological actions of this neuropeptide. The FM-4/TGR-1 receptor is confined almost exclusively to the CNS and its expression is highest in the hypothalamus, especially in the pararaventricular (Guan et al., 2001) and suprachiasmatic nuclei (Nakahara et al., 2004). The paraventricular expression argues for a putative role of the receptor in regulation of the pituitary-adrenal (HPA) axis and feeding, while the suprachiasmatic receptors may govern the sleep/wake cycle and the circadian rhythm of temperature, motor phenomena and hypothalamic hormone (e.g. gonadotropin hormone releasing hormone and corticotrophin releasing hormone CRH) secretion. Moreover, the distribution (abundant hypothalamic expression, mainly in the suprachiasmatic, paraventricular and arcuate nuclei) of NMS the expression itself raises the possibility that, similarly to other neuromedins (and

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especially NMU), it may play a role in the regulation of the above-mentioned hypothalamic functions (Mori et al., 2005, Murakami et al.2005). A recent publication has demonstrated that the expression of NMS is markedly higher than that of NMU in the hypothalamus (Rucinski et al. 2007), which suggests that NMS may predominate in central regulatory processes. Although few data are available as yet regarding its functions, they all reinforce this initial hypothesis. NMS has been demonstrated to influence the circadian rhythm (Mori et al., 2005), feeding (Ida et al., 2005; Shousha et al., 2006) and pituitary luteinizing hormone secretion (Vigo et al., 2006). In the background of these processes, the activation of paraventricular CRH secretion and pro-opiomelanocorotin release from the arcuate nucleus appear to play crucial roles (Ida et al., 2001). These data suggest that other CRH-related endocrine (HPA activation), autonomic (core temperature) and behavioral (anxiety-related motor phenomena) processes may also be influenced by NMS.

We earlier demonstrated that NMS exerted dose-dependent effects on the HPA system, which were inhibited by antalarmin, a CRHR1 receptor antagonist. It also activated grooming and decreased the entries to and time spent in the open arms during the elevated plus maze (EPM) test. The grooming response was abolished by haloperidol and antalarmin pretreatment, while diazepam and antalarmin displayed a tendency to attenuate the response evoked in the EPM test. In superfusion studies, NMS enhanced the release of dopamine from amygdala slices. These results demonstrate that NMS stimulates the HPA axis through the CRHR1 pathway, and evokes stereotyped behavior and anxiety through mesolimbic dopamine and CRH release. (Jászberényi et al.2007)

There have been no published data regarding the action of NMS on learning and memory processes and the possible involvement of certain neurotransmitters in these processes. It has been reported that, outside the hypothalamus, the NMS receptor is found in highest concentrance in the hippocampus, the amygdala, the thalamus and the cerebellum (Raddatz et al, 2000), which suggests its possible role in the regulation of cognitive, emotional and motor phenomena. The aim of the present study was to elucidate the role and action of NMS on fear- motivated learning and memory processes following i.c.v administration and the possible involvement of transmitters in these processes, by pretreatment of rats with receptor blockers.

2. Materials and Methods

2.1. Animals

Male Wistar rats weighing 150-250 g were used.. The animals were kept and handled during the experiments in accordance with the instructions of the University of Szeged Ethical Committee for the Protection of Animals in Research. The rats were kept in their home cages at a constant room temperature on a standard illumination schedule with 12-h light and 12-h dark periods (lights on from 6.00 a.m.). Commercial food and tap water were available ad libitum. The rats were allowed a minimum of 1 week to acclimatize before surgery. To minimize the effects of nonspecific stress, the rats were handled daily.

2.2. Surgery

For i.c.v. peptide, or nitro-L-arginine administration, the rats were implanted with a stainless steel Luer cannula (10 mm long) aimed at the right lateral cerebral ventricle under Nembutal (35 mg/kg, ip.) anaesthesia. The stereotaxic coordinates were 0.2 mm posterior, 1.7 mm lateral to the bregma, 3.7 mm deep from the dural surface, according to the atlas of Pellegrino et al. (1979). Cannulas were secured to the skull with dental cement and acrylate. The rats were used after a recovery period of 5 days. The correct location of the cannula was checked by dissecting the brain following completion of the experiments. Only animals with the correct location of the cannula were used in the evaluation of the experiments. All experiments were performed in the morning period.

2.3. Treatment

The peptide and nitro-L-arginine was given icv. The antagonists of neurotransmitters was given intraperitoneally. Following receptor blockers were used: Atropine sulphate from EGYS (Budapest, Hungary);); haloperidol from G. Richter (Budapest, Hungary); Phenoxybenzamine hydrochloride from Smith Kline & French (Herts, UK); propranolol hydrochloride from ICI Ltd. (Macclesfield, UK); cyproheptadine hydrochloride, from Tocris (Bristol, UK and); naloxone hydrochloride (Endo Labs, Wilmington USA). Nitro-L-Arginine methylester hydrochloride (Sigma St Louis USA). bicuculline methiodide from Sandoz (Basle, Switzerland were obtained. The receptor blockers doses were selected so that the blocker alone were ineffective but were able to block the action of a neuropeptide as described in previous studies (Telegdy et al. 2005 and 2013). Telegdy and Adamik 2013a,b, Tanaka and Telegdy 2014).

2.4.1. Passive avoidance test

One-trial learning, step-through passive avoidance behavior was measured according to Ader et al 1972. Briefly, mice were placed on an illuminated platform and allowed to enter a dark compartment. Since mice prefer dark to light, they normally entered within 5 s. Two additional trials were delivered on the following day. After the second trial, unavoidable mild electric footshocks (0.75 mA, 2 s) were delivered through the grid floor. Having entered the box, the animals could not escape the footshock. After this single trial, the mice were immediately removed from the apparatus and were treated. The consolidation of passive avoidance behavior was tested 24 h later. For consolidation, the animals were treated icv with neuromedin S, 0.5, 1.0 and 2.0 ug. in 2 ul volume. For further test the 2 µg was selected. The receptor blocker was given following the learning trial and 3o min later, the neuromedin S (2 µg). In the 24 h testing each animal was placed on the platform and the latency to enter the dark compartment was measured up to a maximum of 300 s. Each animal was used only once.

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2.5. Statistical analysis

Two way ANOVA test was followed by Tukey's test for multiple comparisons with unequal cell size. Probability values (P) of less than 0.05 are considered significant.

3. Results

The effects of NMS were tested on passive avoidance learning. in doses of 0.5, 1 and 2 µg i.c.v. 2 µg given i.c.v significantly facilitated the consolidation of passive avoidance learning ($F(3,22)= 9.21$; $p<0.05$) while 0.5 and 1.0 µg were ineffective (see figure 1). For combined treatment with each receptor blocker 2 µg i.c.v. was used.

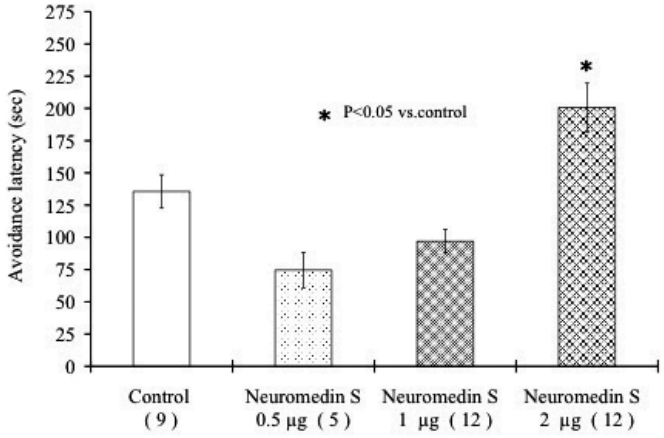

Fig. 1 The effect of different doses of neuromedin S on consolidation of passive avoidance learning. 0.5 and 1.0 μg were not significant in the passive avoidance response, while 2.0 μg i.c.v lenghtened the response. The mean ± S.E.M. are shown. Number in parentheses denote the number of animals used.

Atropine (a nonselective muscarinic acetylcholine receptor antagonist in a dose of 2 mg/kg b.w.,i.p. alone did not influence the test , however fully blocked the NMS (2 µg/ i.c.v.) facilitation of the passive avoidance learning. NMS alone significantly facilitated the passive avoidance learning ($F(3,22)= 10.63$; $p<0.05$; see figure 2)

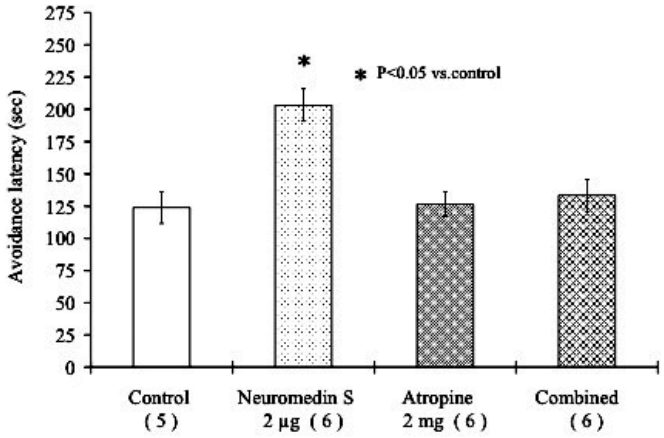

Fig. 2 The effect of nonselective muscarinic acethycholine receptor antagonist, atropine on the neuromedin S-induced (2 ug i.c.v) consolidation of passive avoidance learning (neuromedin S P<0.05 vs. control),combined (atropine 2 mg/kg i.p + neuromedin S 2.0 μg i.c.v). The mean ± S.E.M. are shown. Number in parentheses denote the number of animals used.

Haloperidol (10 µg/kg b.w. i.p.), (a D2 ,D3,D4 dopamine receptor antagonist) did not change the task, however fully blocked the NMS (2 µg/i.c.v) caused facilitation of passive avoidance learning. NMS alone facilitated the passive avoidance memory consolidation ($F(3,23) = 11.45$; $p<0.05$; see figure 3)

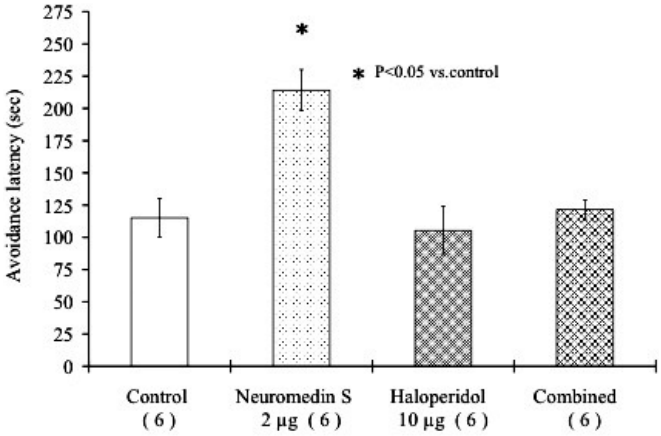

Fig. 3 The effect of a D2,D3,D4 dopamine receptor antagonist haloperidol on neuromedin S (2.0 μg i.c.v.)-induced consolidation of passive avoidance learning.(Neuromedin S *p<0.05 vs control) Combined (haloperidol 10 μg/kg i.p.+ neuromedin S 2.0 μg i.c.v). The mean ± S.E.M. are shown. Number in parentheses denote the number of animals used.

Phenoxybenzamine, (a nonselective α-adrenergic receptor antagonist) treatment (2 mg/kg b.w.,i.p.) alone did not change the task, however blocked the NMS (2 µg/ i.c.v) caused improvement of passive avoidance learning. NMS significantly facilitated the passive avoidance learning ($F(3,22) = 9.49$; $p<0.05$; see figure 4)

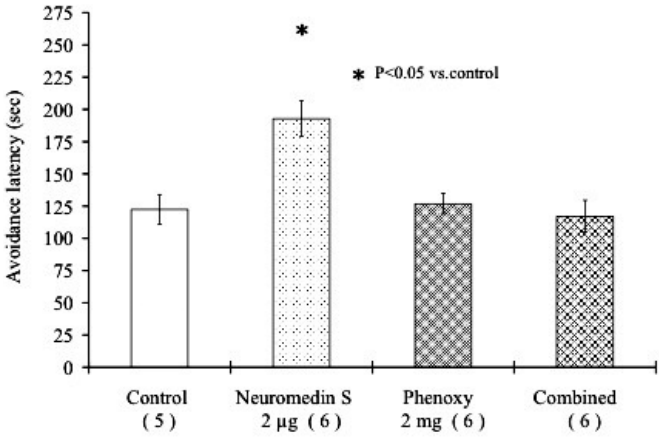

Fig. 4 The effect of a nonselective α-adrenegic receptor antagonist, phenoxybenzamine (Phenoxy) on neuromedin S-induced (2 μg i.c.v) consolidation of passive avoidance learning.(Neuromedin S *P<0.05 vs. control). Combined (phenoxybenzamine 2 mg/kg i.p.+ neuromedin S (2 μg i.c.v). The mean ± S.E.M. are shown. Number in parentheses denote the number of animals used.

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Propranolol (a β-adrenergic receptor antagonist, 5 mg / kg b.w.,i.p) alone had no action on the task, however partially blocked the NMS (2 µg/i.c.v) caused improvement of passive avoidance learning. NMS (2 µg/ i.c.v) alone significantly facilitated the passive avoidance learning ($F(3,21) = 6.40$; $p<0.05$; see figure 5)

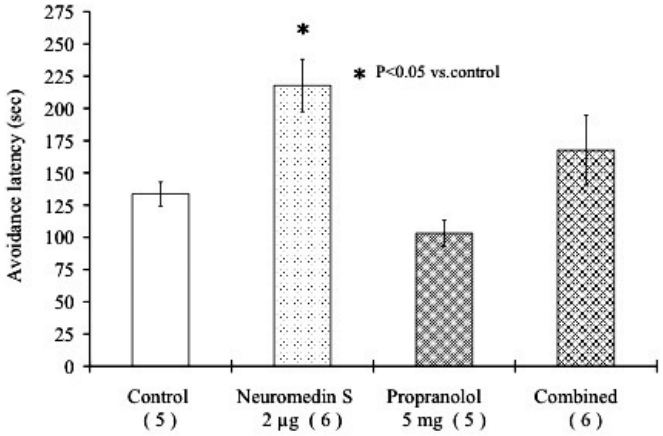

Fig. 5 The effect of β-adrenergic receptor antagonist propranolol on neuromedin S-induced (2 μg i.c.v) consolidation of passive avoidance learning.(Neuromedin S *P<0.05 vs. control). Combined (propranolol 10 mg/kg)i.p.+ neuromedin S-induced (2 μg i.c.v). The mean ± S.E.M. are shown. Number in parentheses denote the number of animals used.

NMS (2 µg/i.c.v) combined with cyproheptadine (a nonselective 5-HT2 serotonergic receptor antagonist, 5 mg/kg b.w.,i.p) pretreatment, cyproheptadine blocked NMS

(2 µg/i.c.v) facilitated the passive avoidance learning. Cyproheptadine had no action alone on the passive avoidance learning. NMS significantly facilitated the passive avoidance learning. ($F(3,22) = 7.88$;$p< 0.05$; see figure 6).

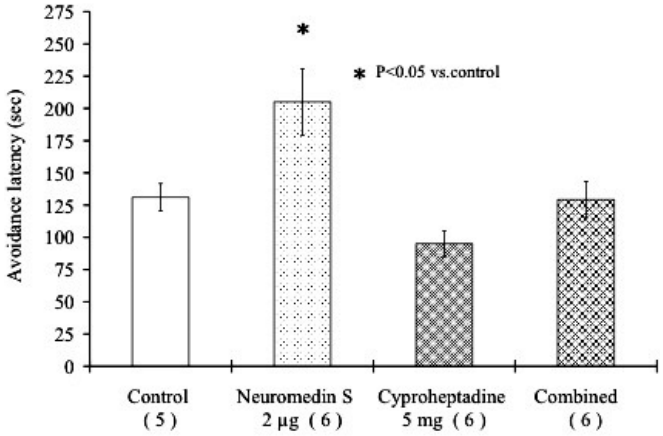

Fig. 6 The effect of cyproheptadine (5 mg/kg i.p.) a non-selective 5-HT2 serotonergic receptor antagonist on neuromedin S-induced (2 μgl i.c.v) consolidation of passive avoidance learning. (Neuromedin S *P<0.05 vs. control). Combined (cyproheptadine 5 mg/kg)i.p.+ neuromedin S (2 μg i.c.v). The mean ± S.E.M are shown. Number in parentheses denote the number of animals used.

Naloxone (0.3 mg/kg, b.w i.p.) a nonselective opioid receptor antagonist) alone had no action on the task, however blocked the NMS (2 ug/i.c.v) caused improvement of passive avoidance learning. NMS alone significantly facilitated the passive avoidance learning ($F(3,20) = 7.38$; $p<0,05$; see figure 7)

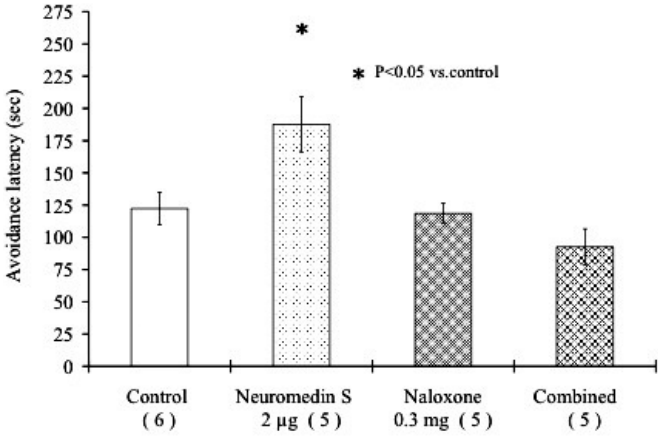

Fig. 7 The effect of a nonselective opioid receptor antagonist, naloxone (0.3 mg/kg i.p.) on neuromedin S-induced (2 μg i.c.v) consolidation of passive avoidance learning. (Neuromedin S *P<0.05 vs. control). Combined (naloxone 0.3 mg/kg i.p)+ neuromedin S (2 μg i.c.v). The mean ± S.E.M are shown. Number in parentheses denote the number of animals used.

Nitro-L-arginine (a nitric oxide synthase inhibitor), (10 µg/kg i.c.v) alone had no action on the task, however blocked the NMS (2 µg/i.c.v) caused improvement of passive avoidance learning. NMS alone significantly facilitated the passive avoidance learning ($F(3,20) = 9.44$; $p<0.05$; see figure 8).

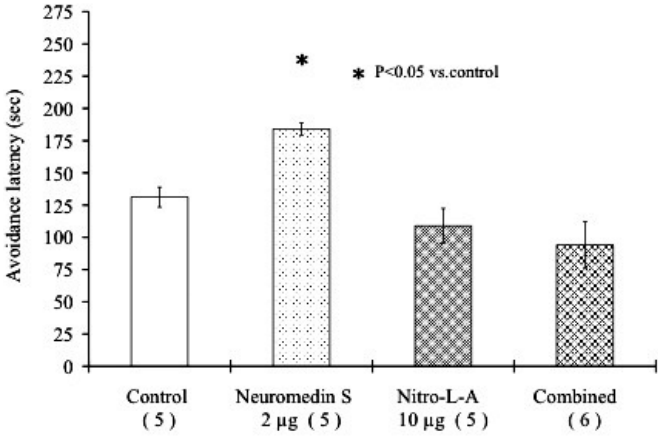

Fig. 8 The effect of a nitro-L-arginine (10 μg/kg i.c.v) (a nitric oxide synthase inhibitor) on neuromedin S-induced (2 μg i.c.v) consolidation of passive avoidance learning. Neuromedin S *P<0.05 vs. control. Combined (nitro-L-arginine 10 μg/kg i.c.v) + neuromedin S (2 μg i.c.v). The mean ± S.E.M are shown. Number in parentheses denote the number of animals used.

Bicuculline (1 mg/kg b.w. .i.p) (a γ-aminobutirc acid subunit (GABA-A) receptor antagonist) did not change the passive avoidance response significantly. Pretreatment with NMS (2 μg/i.c.v) bicuculline did not alter the NMS caused improvement of passive avoidance learning. NMS (2 μg/i.c.v) significantly facilitated the passive avoidance learning (F(3,23)= 3,79 P<0.05; see figure 9)

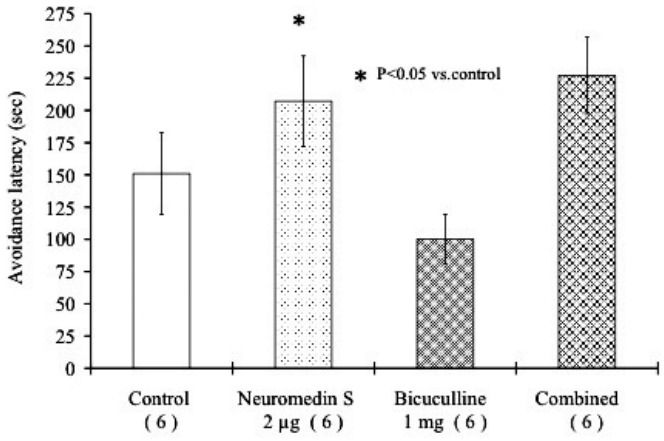

Fig. 9 The effect of a γ-aminobutyric acid subunit A (GABA-A) receptors antagonist bicuculline (1 mg/kg i.p.) on neuromedin S-induced (2 ug i.c.v) consolidation of passive avoidance learning. Neuromedin S *P<0.05 vs. control. Combined (bicuculline 1 mg/kg)i.p.+ neuromedin S (2 μg i.c.v). The mean ± S.E.M are shown. Number in parentheses denote the number of animals used.

4. Discussion

In this paper we demonstrate that NMS facilitate the passive avoidance learning and memory consolidation in rats. This action is mediated by number of neurotransmitters.

A fear-motivated learning, memory consolidation is a rather complex physiological process, which involves motivation, learning, memory consolidation, movement etc . It is generally accepted that neuropeptides are acting mainly as neuromodulators changing the activity of certain transmitters, however usually the transmitters involved in these processes are very seldom studied. In our previous study we proved that dopamine is important in the NMS action on HPA axis, grooming response, and anxiety. Furthermore in vitro superfusion study with NMS enhances dopamine release from the amygdale slices (Jászberényi et al 2007).

Comparing the transmitter mediation in passive avoidance response with other neuropeptides, although they are structurally different, the outcome of facilitating the passive avoidance response are the same, the transmitters are differ. Urocortin 1, apelin-13, kisspeptin-13 and NMS all are using cholinergic, α-adrenergic, serotonergic transmissions and the last 3 peptides, nitric oxide .The first 3 are using GABA-A receptors, however NMS is not. Nitric oxide has been used for apelin-13, kisspeptin-13 and NMS, however for urocortin1 is not. Dopaminergic receptor is used with the exception of kisspeptin-13 for all other three neuropeptides (Telegdy et al. 2005, 2013, Tanaka and Telegdy 2014, Telegdy and Adamik 2013ab) . These similarities and dissimilarities suggest that these peptides utilizing different neurotransmitters which finally will lead to a learning and memory processes. The exact nature of this details are at the present poorly understood. If we will know exactly all details (fear, motivation, movement, hormonal background etc) we could localize the side of action in term of transmitter interaction.

The close structural relation with neuromedin U (NMU) our previous work give a chance to compare the similarities and dissimilarities in action of the two neuropeptides Both peptides facilitate the activity of the pituitary-adrenal cortex (Jászberényi et al 2007, Ida et al.2005), however NMU is anxiolytic (Telegdy and Adamik 2013b) while NMS is anxiogenic (Jászberényi et al 2007). The transmitter mediation is not studied for NMS in depression and anxiety , while we have done it for NMU. (Telegdy and Adamik 2013b, Tanaka and Telegdy 2014). Further studies with NMS on anxiety and depression could explain the difference in receptor affinity which can be observed between NMS and NMU.

5. Acknowledgements.

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