Theoretical Medical Sciences Ph.D. Program

THE ROLE OF NEUROTENSINERGIC MECHANINISMS IN THE REGULATION OF BEHAVIOURAL PROCESSES

Ph.D. Thesis

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1. INTRODUCTION

Neurotensin (NT) acts as a neurotransmitter and/or neuromodulator in the central nervous system. It has been shown that there is a relationship between malfunction of the NT system and several neurologic and psychiatric diseases, i.e: schizophrenia, Parkinson's disease, mood disorders and drug addiction. NT has been proven to have positive reinforcing effects in the ventral tegmental area (VTA) and it can modify the place learning process in the nucleus accumbens (NAC).

The central nucleus of amygdala (CeA), part of the limbic system, plays an important role in learning, memory and reinforcement. It was published that the CeA is relatively rich in NT immunoreactivity, it contains neurotensin-1 receptors (NTS1) in high density, however, behavioural effects of NT were not examined in this brain structure yet. We studied the possible effects of NT microinjected into the CeA in reinforcing mechanisms, learning and memory processes.

Therefore the topic of this thesis is the examination of neuropeptide NT induced behavioural effects in the CeA in rats. The effects of this neuropeptide on reinforcement was investigated in conditioned place preference test. Anxiety was studied in elevated plus maze test. Morris water maze test was used to examine the possible effect of NT on spatial learning and memory consolidation and retention were investigated in passive avoidance paradigm. The possible effect of NT on spontaneous motor activity was investigated in open field test. Furthermore, receptorial mechanisms and neurotensinergic-dopaminergic interaction were examined in order to understand the complex behavioural effects of NT.

2. OBJECTIVES

a. The mesolimbic dopamine (DA) system originates from the VTA and one of its abundant terminal fields is localized in the CeA. It has been shown that NT injected into the VTA has positive reinforcing effects. The CeA is rich in NT

terminals and NTS1s. Therefore, our first goal is to examine whether NT in the CeA has positive reinforcing effects in **conditioned place preference test**.

b. In case of positive reinforcing effects, in the place preference test animals spend more time in a certain part of the apparatus than in the others. This could also be due to an anxiogenic effect of the neurochemical substance received, when the animals decrease their movement activity and they are motionless in a freezing positure. Therefore, we examine whether NT microinjections into CeA have any effects on anxiety in the **elevated plus-maze test**.

c. It is known that the amygdala plays an important role in learning process including place learning. Moreover it was proven that in some brain structures the blockade of the neurotensinergic system resulted in place-learning difficulties. Therefore, we study the effects of NT and NTS1 antagonist in **Morris water maze test.**

d. Amygdala is thought to be a key structure in formation of fear-conditioned learning. Memory enhancing effects of NT in passive avoidace paradigm were shown in some brain structures. Therefore, we investigate the possible effects of NT and NTS1 antagonist in **passive avoidance test**.

e. Numerous studies have suggested that there is anatomical and functional relationship between the neurotensinergic and dopaminergic systems. It is known that the mesocortical-mesolimbic DA system, which innervates the amygdala, plays a crucial role in reinforcement and learning. We suppose that NT exerts its reinforcing, learning and memory enhancing effects via modificating the activity of the DA system. Therefore, we examine NT-DA interaction in **condtitioned place preference test,** in **Morris water maze test** and in **passive avoidance test** by applying DA D2 antagonist preteatment before NT microinjection.

f. If the NT microinjected into the CeA influences the general motor activity this effect can modify learning releated effects of NT examined in different behavioural paradigms. Therefore, we investigate the possible motor activity modulating effects of NT, NTS1 antagonist and DA D2 antagonist in **open field test**.

3. MATERIALS AND METHODS

3.1. Subjects

Four hundred and forty adult male Wistar rats weighing 280–320 g at the beginning of the experiments were housed individually and cared for in accordance with institutional (Pécs University, Medical School) and international standards (European Community Council Directive - 1986. November 24. 86-609-EEC). Rats were kept in a temperature- and light-controlled room (22 ± 2 °C; 12:12 h light–dark cycle with lights on at 6:00 a.m.). Standard laboratory food pellets (CRLT/N standard rodent food pellet, Charles River Kft, Budapest, Hungary) and tap water were available ad libitum. All behavioural tests were done during the rats' daylight period between 08:00 and 18:00 h.

3.2. Surgery

Rats were anesthetized i.p. by ketamine supplemented with diazepam (Calypsol and Seduxen, Richter Gedeon, Hungary, ketamine: 80 mg/kg body weight, diazepam: 20 mg/kg body weight). Animals were stereotaxically implanted bilaterally with 22 gauge stainless steel guide cannulae, directed toward and 1 mm above the dorsal border of the CeA (coordinates relative to bregma: AP: −2.3 mm, ML: ±4.1 mm, DV: −6.5 mm) according to the rats' stereotaxic atlas [46]. Cannulae were fixed to the skull with two stainless steel screws and dental acrylic. When not being used for injection, the guide cannulae were occluded with 27 gauge stainless steel obturators. Animals were allowed a minimum of 6 days postoperative recovery before experiments commenced while they were handled daily.

3.3. Materials

NT obtained from Sigma (Sigma–Aldrich Co., N 3010) was bilaterally microinjected in two different doses: 100 ng (54.6 pmol) or 250 ng (136.6 pmol) in 0.4 μl, respectively. NT was dissolved in 0.15 M sterile saline solution containing 0.01 M Na-acetate and 0.01 M phosphate buffered saline (PBS, pH 7.4). Control animals

received this solution bilaterally as vehicle (Veh1) in equal volume to that used for NT injections. NTS1 antagonist SR 48692 [gifted by Sanofi-Synthelabo Co., 35 ng (60 pmol)/0.4 µl] was diluted in 0.15 M saline solution containing 2% dimethylsulfoxide and 0.01 M PBS, and its vehicle solution (Veh2) was used for control injections in the experiment with NTS1 antagonist. In this experiment the following groups were used: the antagonist treated group (ANT) received SR 48692 and then 15 min later vehicle of NT (ANT + Veh1). The NT injected group pretreated with antagonist (ANT + NT) received SR 48692 15 min before being injected with 100 ng NT. The NT treated group (NT) received vehicle of antagonist and then 100 ng NT (Veh2 + NT). The control group (Control) received two vehicle injections (Veh2 + Veh1). The antagonist or Veh2 were applied 15 min prior to NT or Veh1 injections, respectively. DA D2 receptor antagonist Sulpiride: [Sigma_Aldrich Co.:S7771[S] 5 µg (14.6 nmol)] was dissolved in 0.1 M HCl diluted with distilled water and it was set to 7.4 pH with NaOH and phosphate buffer. This diluting solution (Veh3) was injected to the adequate control groups. Solutions were kept in +4 °C before application. In this report all the doses mentioned are meant to be the dose per side values. Drugs or vehicles were bilaterally microinjected through a 30 gauge stainless steel injection tube extending 1 mm below the tips of the implanted guide cannulae. The injection cannula was attached via polyethylene tubing (PE-10) to a 10 µl Hamilton microsyringe (Hamilton Co., Bonaduz, Switzerland). All injections were delivered by a syringe pump in volume of 0.4 µl (Cole Parmer, IITC, Life Sci. Instruments, California) over a 60 s interval. After injection cannulae were left in place for an additional 60 s to allow diffusion into the surrounding tissue. During the injections rats were gently hold in hands.

3.4. Behavioural experiments

3.4.1. Conditioned place preference (CPP) test

The CPP paradigm has been used to measure hedonic properties of drug abuse as well as natural reinforcers [43]. Our corral apparatus consisted of a circular open field, with a diameter of 85 cm and 40 cm high wall. Black lines divided the floor into four quadrants of equal size. External visual cues in the surroundings helped the animals' spatial

orientation inside the apparatus. The room was dimly lit by a 40W bulb. The place preference procedure consisted of one habituation (day 1), two conditioning (day 2-3) and one test (day 4) trials, each lasted for 900 s (15 min). The apparatus was cleaned and dried after each session. All trainings and testing were conducted in an isolated experimental room. In habituation trial (day 1) animals were placed into the apparatus and had free access to all parts of the apparatus for 900 s. The time that animals had spent in each of the four quadrants was measured. During conditioning trials (day 2-3) animals received the drug injections and subsequently rats were restricted to the treatment quadrant for 15 min by means of a plexiglass barrier. Treatment quadrant (TQ) was determined to be one of the four quadrants in which the animal had spent neither the longest nor the shortest time during habituation. On the fourth day (test trial) animals had free access to all parts of the apparatus. The time that rats had spent in each of the four quadrants was measured again. Behaviour of animals was recorded by a video camera. Data were stored and motion analysis was made by means of EthoVision Basic software (Noldus Information Technology b.v., Wageningen, The Netherlands). The number of entries into the four quadrants was also recorded during habituation and test trials, as a measure of gross locomotor activity. In order to gauge acute effects of NT on spontaneous behaviour, frequency of rearing and grooming were also analyzed.

3.4.2. Elevated plus maze (EPM) test

Anxiety was evaluated in an elevated plus maze (EPM) test [17]. The apparatus was constructed of grey coloured wooden planks. The equipment consisted of two opposite open arms (50x12cm) and two opposite enclosed arms (50x12x40cm) with an open roof. The maze was elevated to a height of 100 cm above the floor. After drug administrations the animals were placed into the center of the maze (central platform), facing one of the enclosed arms. The trials lasted for 5 min while the number of entries into and time spent on the open and enclosed arms and the end of the open arms (end-arms) were measured. Each rat was tested only once. Data were stored and motion analysis was made by means of EthoVision Basic software.

3.4.3. Morris water maze (MWM) test

Tests [29] were made in a circular pool with a diameter of 1.5 meter. The pool was filled with water (temperature: 23 ± 1 °C) and a square (10cmx10cm) plexiglass platform was placed in. The surface of the water was kept 2 cm above the platform and the water was coloured to make the water opaque. The pool was surrounded with external cues. These cues were kept in constant positions throughout the whole experiment. Behaviour of animals was recorded by a video camera and registered by a computer program (EthoVision; Noldus Information Technology, The Netherlands). The latency time to find the safe platform located in one of the quadrants of the maze was measured. One day before starting the training, rats were habituated to the pool by allowing them to perform swimming for 90 s without platform. During conditioning for spatial learning, rats were placed into the water maze for two trials per day for two days (trial 1 and trial 2 were performed on the first day before the NT administration, trial 3 and trial 4 were made on the second day after the injection) at randomly assigned, but predetermined locations. The task required rats to swim to the hidden platform guided by external spatial cues. After finding the platform, rats were allowed to stay there for 10 s. Rats failing to find the platform in 180 s were placed on the platform and allowed to rest for 10 s.

3.4.4. Passive avoidance (PAV) test

A step-through avoidance paradigm was used in a two compartment passive avoidance apparatus. The experimental apparatus consisted of a large (60 cm × 60 cm × 60 cm), well illuminated (Tungsraflex, 100 W) compartment and a small box (15 cm × 15 cm × 15 cm), painted black and having metal-grid floor for the delivery of electric shocks. Rats were habituated on the 1st day of the experiment when they were placed into the large compartment and were allowed a maximum time of 180 s to enter the dark compartment. On the following day animals were *conditioned.* Subjects were placed again into the illuminated compartment and latency to enter the shock box through a guillotine trap door was measured. After rats had entered the dark box, they were given electric foot shock three times, each for 1 s with weak (0.4 mA) electric current. Subsequently rats were removed from the apparatus and were microinjected

bilaterally. Animals were injected in their home cage. The same rats were *tested* 24 h (test 1) and 1 week after (test 2) *conditioning* and the latency of entering the shock box was recorded. When the animal had not entered the shock box till the end of the trial the maximum value was given (180 s). Data were recorded and evaluated by means of the Noldus Ethovison System (Noldus Information Technology, The Netherlands).

3.4.5. Open field (OPF) test

Animals were placed into 60x60x60 cm painted grey box after bilateral microinjections. The ground of the cage was divided into 16 identical squares. Behaviour of each rat was recorded for 5 minutes by means of CCD camera. During observation period the number of crossings and the distance moved were investigated. Data were stored and analysed by Noldus Ethovision System.

3.5. Data processing

3.5.1. Histology

At the end of the experiments, rats received an overdose of Calypsol and Seduxen mixed in the ratio of 4:1 and were transcardially perfused with isotonic saline followed by 10% formalin solution. After 1 week of postfixation brains were frozen cut into 40 μm serial sections and stained with Cresyl-violet. Injection sites were reconstructed according to the stereotaxic atlas of the rat brain [46]. Only data from rats with correctly placed cannulae were analyzed.

3.5.1. Statistics

Data are presented as mean ± standard error of the mean (S.E.M.). One-way and two-way ANOVAs followed by Tukey post hoc analysis were employed (ANOVA GraphPad InStat for Windows 3.0). Statistical significance was established at $p \leq 0.05$.

4. RESULTS

4.1. Conditioned place preference test

It has been proven in the CPP test that NT microinjected into the CeA has positive reinforcing effects. Rats that received 100 ng NT or 250 ng NT spent significantly more time in the TQ during the *test* session. The positive reinforcing effect of NT might be mediated via NTS1, since this effect could be blocked by NTS1 antagonist pretreatment. The rewarding effect of NT may be due to the modulation of DA system, since it could be blocked by DA D2 antagonist preteatment.

4.2. Elevated plus maze test

The possible anxiogenic or anxiolytic effects of NT was investigated in EPM test. The test was carried out after bilateral 100 ng NT or 250 ng NT or vehicle injections. There were no differences among groups, as far as the measured parameters concerned, i.e. the time spent in the open arms or in the end arms or in the numbers of entries into the open arms. Therefore, our results suggest that neither 100 ng NT nor the 250 ng NT had effects on anxiety in the CeA.

4.3. Morris water maze test

MWM test was used to examine the possible modulatory effects of NT on spatial learning. Statistical evaluation of this experiment indicated that the intraamygdaloid microinjection of NT resulted in considerable alteration of learning in MWM. The multiple comparison after the NT treatment (trials 3 and 4) yielded that the 100 ng NT and 250 ng NT treated animals needed significantly less time to find the safe platform than the controls. The multiple comparison also indicated that 100 ng NT treated rats needed significantly less time to find the platform than the vehicle or ANT or ANT + 100 ng NT treated rats. Effect of 100 ng NT was eliminated by bilateral intraamygdaloid pretreatment of ANT. Our results are the first to demonstrate that NT

facilitates spatial learning when microinjected into the CeA. The effect of NT is specific because it can be blocked by prior application of NTS1 antagonist. Moreover spatial learning enhancing effects of NT could be blocked by prior treatment of DA D2 antagonist.

4.4. Passive avoidance test

Improvement in passive avoidance learning by NT in the CeA was evident when the PAV test was carried out. Application of 100 ng NT significantly increased the latency time (the latency to enter the dark shock compartment) 24 hours and 1 week after conditioning. Effect was NTS1 specific because prior treatment with the NTS1 antagonist, equimolar to NT treatment blocked the effects of NT. DA system may play a role in NT induced passive avoidance learning because DA D2 antagonist could block this action. On the other hand, rats received 250 ng NT, showed only a tendency for learning.

4.5. Open field test

OPF test was used to measure the spontaneous motor activity after bilateral microinjections. The following groups were tested: 100 ng NT-, 250 ng NT-, ANT-, ANT + NT-, DA D2 antagonist-, DA D2 antagonist + NT and vehicle treated animals. In each group behavioural results after treatments were compared to data obtained one day before microinjection. The distance moved and the number of crossings were evaluated. There were no significant difference in the measured parameters.

5. DISCUSSION

5.1. Conditioned place preference test

Our findings indicate that NT microinjected into the CeA has positive reinforcing effects which are comparable to those results obtained after NT microinjections into other

brain (limbic) structures. Namely, it has been shown that NT microinjected into the VTA or ventral mesencephalic region has positive reinforcing properties in CPP paradigm [13,36]. It was also proven with direct intracerebral self-injection studies that NT is a positive reinforcer in the VTA [12].

The CeA, part of the limbic system, plays an important role in memory [28] and reinforcement [22,25] and it was shown that it is relatively rich in NT immunoreactive elements and NTS1s [6,9,31,45]. One may suppose that direct application of NT can influence the firing of CeA neurons. Indeed an in vitro study indicated that 60% of the CeA neurons showed excitatory responses while 9% of the cells examined showed inhibitory ones to application of NT [26]. In our experiments excitatory and/or inhibitory single neuronal responses were recorded after electrophoretic or micropressure application of NT in the CeA in anesthetized rats. Based on these results it is obvious that NT as a neuromodulator may directly modify the activity of CeA neuronal network.

It is known that NT has the highest affinity to NTS1 [24,45]. In our experiments we used SR 48692 because this is a selective non-peptide NTS1 antagonist and it can have effects on the NT induced behaviour [40]. Our findings showed that NTS1 plays important roles in the positive reinforcing effects, because pretreatment with NTS1 antagonist could block this action. The NTS1 antagonist SR 48692 was applied 15 min prior to the NT microinjection so this chemically stable antagonist could have enough time to bind to the NTS1s.

Some neuropeptides like substance P and NT are thought to have positive reinforcing effects through the modulation of the mesolimbic DA system [21]. A relationship seems to exist between the neurotensinergic and dopaminergic systems. Biochemical and electrophysiological studies have shown that NT changes the activity of DA neurons in the substantia nigra (SN) or VTA and facilitates endogenous DA release from rat slices of the striatum, NAC and prefrontal cortex [16,27,35]. Several electrophysiological studies indicate that NT increases the firing frequencies of DA neurons in vivo and in vitro. It has been shown that NT stimulates DA neuronal firing rate respectively in the SN the VTA and frontal cortex pyramidal neurons [19,34,38]. Furthermore it has been suggested that NT may be colocalized with DA in the same vesicle [4,5]. We suppose that NT microinjected into the CeA has a positive reinforcing effect through the

modulation of the mesolimbic DA system. In our experiment DA D2 receptor antagonist pretreatment could block the effect of NT induced positive reinforcement

5.2. Elevated plus maze test

EPM test was made for two reasons: AMY, as part of the limbic system, plays a crucial role in fear related behaviour, anxiety and in their reinforcing mechanisms. Since the AMY is relatively rich in NTS1s we would have liked to investigate whether the NT injected into the CeA may play a role in anxiety. On the other hand, one may suppose that animals spent more time in TQ because of the possible anxiogenic effect of the microinjected drug. Our results proved that NT microinjected into the CeA in EPM had neither anxiogenic nor anxiolytic effects. Our findings contradict to the possibility that animals were less active after NT treatments because there were no statistical differences among the groups in the gross locomotor activity, nor in the numbers of entries into the TQ. Consequently it can be stated that in the CPP paradigm the longer time animals spent in the TQ was not due to any anxiogenic effects of NT.

5.3. Morris water maze test

The MWM test is a widely used appropriate method to investigate spatial learning. The size of our pool corresponded to that used by others [29]. During experiments rats were placed into the water maze for two trials per day for two days. According to the literature the number of trials used in MWM test and the number of daily trials show high variability [1,7,23,30]. As observed in our previous experiments, rats learn quickly [42]. Therefore, it is adequate to study the possible learning/memory enhancing effect of a substance in a schedule with a relatively limited number of trials. The many days- many trials paradigm is a more appropriate method to study memory impairment [30]. Under the condition of our experiments a weak learning effect or a learning tendency could be evoked in controls and the possible spatial learning enhancing effect of NT could be examined. It was indicated that the memory consolidation takes place after the experience

[18]. Furthermore, the other benefit of the post-trial injection is the improbability that anxiety, pain or other non specific performance variables are involved in the effect of a given neurochemical substance. Therefore, the subsequent post-experience injection of NT is the most accurate method to study the possible memory enhancing effect. According to our best knowledge no data are available about the possible effect of NT on spatial learning in the AMY. In our experiment escape latency was significantly reduced by 100 ng NT or 250 ng NT, therefore spatial learning enhancing effect was observed. Numerous studies indicate that NT plays a role in reinforcement and learning [13,36,37,41]. As far as we know, our results are the first suggesting that intraamygdaloid NT enhances spatial learning processes and memory. Neither the average speed of swimming during the trials, nor the distance swum during the habituation trial differed significantly among animals as it was calculated by means of Noldus EthoVision program. Consequently our results can not be explained by any alteration in motor activity of rats. In our present experiments we used SR 48692 because this is a selective non-peptide NTS1 antagonist and it can block NT induced actions [14,32,33]. It was proven that high dose of SR 48692 in itself can influence learning and memory because its microinjection into the nucleus accumbens impaired spatial learning [41]. As our results indicated NTS1 antagonist microinjected into the CeA -in itself- did not have any significant effect in the dose used in our experiment. Our findings showed that NTS1 plays an important role in the spatial learning enhancing effects of NT, because pretreatment with NTS1 antagonist could block this action. In conclusion our results are the first to demonstrate that NT facilitates spatial learning when microinjected into the CeA. The effect of NT is specific because it can be blocked by prior application of NTS1 antagonist. The spatial learning enhancing effect of NT may be due to the modulation of DA system, since it could be blocked by DA D2 antagonist pretreatment. The exact mechanisms through which NT can exert its spatial learning facilitating effects, however, needs further investigations.

5.4. Passive avoidance test

In our experiment NT showed learning improvement in PAV test when it was microinjected into the CeA. Under natural circumstances rats like dark and closed places. Animals were punished after they had entered the shock box with painful electrical shocks during the conditionig trial. It has been proven earlier that NT plays a role in pain-transmission [8]. This may indicate that NT increases the latency time in PAV by modulating the pain-transmission instead of affecting the memory consolidation and retention. To avoid this possibility NT was microinjected after the application of electeric shock.

Our data indicated that the application of 100 ng NT significantly increased the latency time but in those rats who received 250 ng NT only a learning tendency was observed. It was proven before that NT may show a bell-shaped dose-effect curve [39]. This phenomenon could be due to the rapid internalization- and intracellular degradation of NTS1 [15,44]. Furthermore, it was published that NTS1 desensitisation and down-regulation are rapid [2,10].

Our findings showed that NTS1 plays an important role in the passive avoidance learning enhancing effects of NT, because pretreatment with NTS1 antagonist could block this action. Furthermore we suppose that NT has a positive reinforcing effect through the modulation of the mesolimbic DA system because DA D2 receptor antagonist pretreatment could block this learning enhancing effect.

5.5. Open field test

Open field test is an appropriate method to investigate general motor activity. Possible effect of NT on motor activity may have many aspects. On one hand, we have shown that in CPP that NT microinjected rats spend more time in the TQ. One may suppose that this effect could be due to hypoactivity. On the other hand, the alteration in motor activity may modify latency time measured in PAV paradigm and MWM test.

Contradictory data can be found, however, about the effects of NT on motor activity. While NT microinjections into the VTA increased the spontaneous motor activity [20],

NT could block the amphetamine induced hyperactivity in the NAC and NT in itself reduced the open field activity [3,11]. In our experiments 100 ng or 250 ng NT microinjected into the CeA did not influence spontaneous locomotor activity or other characteristic behavioural phenomena such as rearing, grooming or freezing.

6. Summary

1., Application of 100 ng NT or 250 ng NT into the CeA has positive reinforcing effects. Our findings show that NTS1 plays an important role in positive reinforcement, because preteatment with NTS1 antagonist could block this action.

2., Positive reinforcing effect of NT could be blocked by DA D2 antagonist pretreatment.

3., Our results showed that NT microinjected into the CeA in EPM had neither anxiogenic, nor anxiolytic effects. Consequently, it can be stated that in the CPP paradigm the more time that animals spent in the TQ was not due to any anxiogenic effects of NT.

4., NT was shown to facilitate the spatial learning in MWM test. This action is NTS1 specific.

5., DA D2 antagonist pretreatment could block the spatial learning enhancing effect.

6., Our results showed that NT microinjected into CeA plays a role in passive avoidance learning. This effect could be blocked by NTS1 antagonist pretreatment.

7., It was shown that memory enhancing effect of NT could be eliminated by prior treatment of DA D2 antagonist.

8., We demonstrated that NT has no effect on spontaneous motor activity. Therefore, the positive reinforcing effect-, the learning- and memory enhancing effects of the NT can not be due to changes in general motor activity. NTS1 antagonist or DA D2 antagonist in itself did not influence the open field activity.

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8. LIST OF PUBLICATIONS

7.1. Publications related to this thesis

K. Laszlo, K. Toth, E. Kertes, L. Peczely and L. Lenard, The role of neurotensin in positive reinforcement in the rat central nucleus of amygdala, Behav. Brain Res. 208 430-435. (2010) **(IF:3,171)**

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7.2. Further publications

K. Toth, **K. Laszlo**, E.E. Bagi, E. Lukacs and L. Lenard, Effects of intraamygdaloid microinjections of acylated-ghrelin on liquid food intake of rats, Brain Res. Bull 77 (2008) 105-111. **(IF:2,281)**

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