CENTRALLY APPLIED OXYTOCIN HAS NO EFFECT ON EYELID CONDITIONING IN RABBITS

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Objective. The classically conditioned rabbit eyelid reflex has proven to be useful for studying memory processes. The role of oxytocin (OXT) dialyzed into the hippocampus or caudate nucleus in the acquisition and extinction of this reflex was investigated.

Methods. Microdialysis probes were unilaterally, chronically, alternatively implanted into the mentioned brain structures. OXT was repeatedly dialyzed into each brain structure during the extinction of the conditioned eyelid reflex. An air puff was applied as an unconditioned and the tone as a conditioned stimulus to create conditioned eyelid reflex. Eyelid responses were detected by opto-electronic sensor and recorded. Thus obtained conditioned responses were calculated as a percentage of all 120, daily applied, trials of stimuli. ANOVA was used for statistical evaluation.

Results. Neither OXT dialyzed into the hippocampus nor into the caudate nucleus significantly changed the course of acquisition and extinction of the conditioned eyelid reflex. However, some tendency to the impairment of forgetting when dialyzed into the hippocampus and to its facilitation during caudate nucleus dialysis was observed.

Conclusion. Conditioning of the eyelid reflex applied as the experimental model for the study of the memory processes did not show OXT participation in these processes neither in the hippocampus nor in the caudate nucleus, but this problem needs to be further studied.

Key words: Conditioned eyelid reflex – Oxytocin – Hippocampus – Caudate nucleus – Microdialysis – Rabbit

Oxytocin (OXT), in addition to its peripheral hormonal effects in mammals, may act as a neurotransmitter and/or neuromodulator in various areas of the central nervous system. In this paper we focus on OXT function in learning and memory.

A general view exists on OXT as a naturally occurring amnesic neuropeptide, because it affected active and passive avoidance behaviour in an opposite direction to vasopressin, that is slightly impaired acquisition and accelerated extinction in rats (BOHUS et al. 1978). However, following higher doses, this effect disappeared or an opposite effect was observed (BOHUS et al. 1978). It can be seen that passive avoidance data are much more conflicting than active avoidance data (DE WIED et al. 1991; SAHGAL and WRIGHT 1984). Effect of OXT in passive avoidance in mice depended on the time of treatment (BOCCIA et al. 1998). Social recognition behaviour also provided conflicted data on OXT participation in memory processes. Social memory was attenuated or facilitated by OXT depending on the dose of the peptide (POPIK and van Ree 1998). Impairment of memory performance after OXT treatment was observed in humans (FEHM-WOLFSDORF et al. 1984).

Some behavioural effect such as the impairment of acquisition in active avoidance behaviour in rats was observed after intrahippocampal administration of OXT (IBRAGIMOV 1990). It may indicate the hip-

pocampus as the basic structure for OXT action in learning. An opposite conclusion follows from the experiments by HESS et al. (1992) in rats selectively bred for differences in behavioural performance. No significant differences were observed between OXT concentrations in the hippocampus of the low behavioural performance rat line and high behavioural performance rat line (HESS et al. 1992).

The objective of the present study was to examine if OXT dialyzed into the hippocampus affects memory processes in rabbits and if its action depends on the applied concentrations of this peptide. Classical conditioning of the rabbit eyelid reflex was used as the model of learning. The hippocampus does not play an essential but a modulatory role in this form of learning (BERGER and THOMPSON 1978) and consistent eyelid conditioning-specific hippocampal changes were shown (SANCHEZ-ANDRES and ALKON 1991).

The caudate nucleus was also dialyzed with OXT as the reference structure for the hippocampus. This nucleus belongs to the basal ganglia traditionally considered to be involved in the control of movements. It is a rather large structure, of the various subcortical structures possibly important for conditional motor reflexes (SADOWSKI 1959) including conditioned rabbit nictitating membrane (equivalent to the eyelid) reflex (RICHARDSON and THOMPSON 1985). There is some evidence suggesting that the caudate nucleus may be involved in the acquisition and retention of skills or habits (DECOTEAU and KESNER 2000). Pharmacological study proved the involvement of caudate nucleus in memory consolidation in the Morris Water Maze (SETLOW and MCGAUGH 1999). Moreover, in awake rats neurons located in the caudate nucleus responded to peripheral sensory stimulation including auditory stimuli (SCHNEIDER 1991).The hypothesis exists that a corticostriatal system with caudate nucleus, and hippocampal or fornix/fimbria system contribute to different forms of learning. The first mediates stimulus-response habit formation whereas the second contributes to cognitive-spatial learning (PETRI and MISHKIN 1994).

Materials and Methods

Animals and surgery. The experiments were carried out in 23 adult male white New Zealand rabbits, at least four months old, weighing over 3 kg. They were housed in single cages in a light regulated (lights on 06.00 h and off 20.00 h) room with continuous access to food and water. All experimental procedures were carried out in accordance with the NIH guide for care and use of the laboratory animals.

Surgical procedure (implantation of guide cannulas for dialysis probes) was carried out under pentobarbital anaesthesia (30 mg/kg). The rabbits were additionally premedicated with a subcutaneous injection of atropine sulphate (1.0 mg/animal). The procedure of guide cannulas implantation and microdialysis of brain structures was described in detail by TRACZYK et al. (1997). After reaching deep surgical anaesthesia the animal was mounted on the stereotaxic frame (SAWYER 1954) and stereotaxically implanted with a plexiglass headpiece with guide cannulas: two leading to the caudate nuclei and two others leading to the hippocampi. The fifth cannula leading to the 3rd cerebral ventricle was used as a reference point. It's tip was positioning 10 mm deep from the surface of the dura mater. The guide cannulas leading to the caudate nuclei and to the hippocampi were positioned 6 mm and 8 mm, respectively laterally on either side of the sagittal zero plane. Typical positions of the probes' tips in the brain structures are shown in Fig. 1. After surgery the rabbits received intramuscular injection of 100,000 IU of benzylpenicillin potassium and 0.5 g streptomycin daily for five consecutive days.

The animals were allowed to recover for at least 1 month prior to the commencement of behavioural experiments.

Training and testing procedures. A special device, called Phonopneumatic stimulator, was used for the acquisition and extinction of the eyelid reflex. The apparatus and whole procedure were described earlier (Orlowska-Majdak et al. 2001 a). It generated periodic air puffs and tones and controlled the recorder. The air puff, used as an unconditioned stimulus (US), exerted a pressure of 0.2 kg/cm^2 and lasted 100 ms, the tone generated by the apparatus, used as a conditioned stimulus (CS), was 1 kHz, 70 dB and lasted 450 ms. Photoelectric transducer detecting in close infrared converted the movements of rabbit's eyelid into electric signals. When the rabbit's eye was completely closed, maximum light emitted by an infrared light emitting diode (LED)

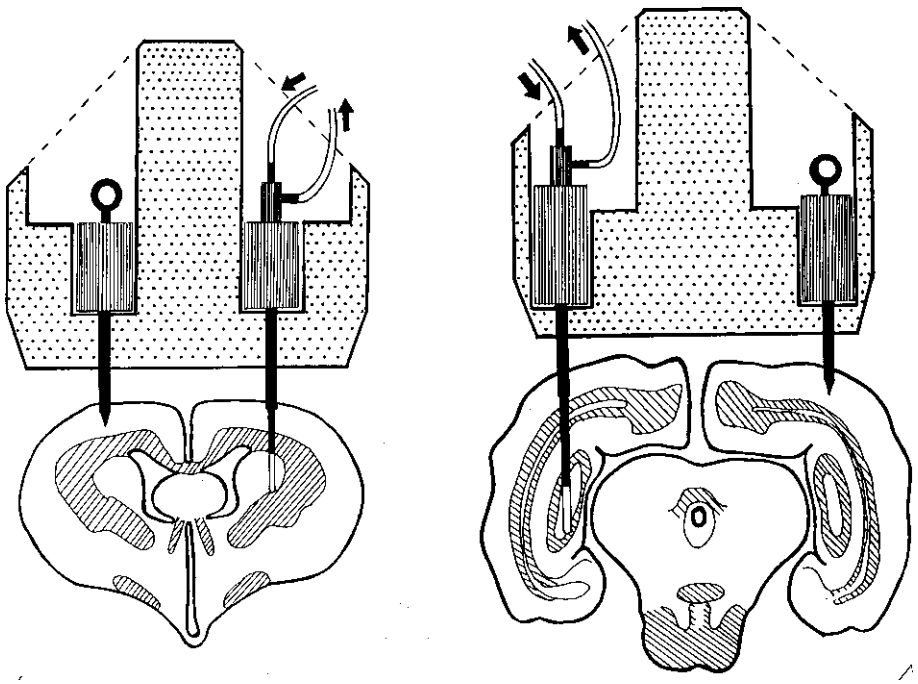

Fig 1 Frontal sections of rabbit's brain in P8 (on the right – hippocampus) and A1 (on the left – caudate nucleus) and the headpiece with position of microdialysis probe. Arrows indicate outflow and inflow of the fluid perfusing the microdialysis probe. Stilettes in the guide cannulas are shown contralaterally to the probes. Plane modified from the Sawyer et al. (1954) atlas.

was reflected from the eyelid and the maximal amplitude of the response was observed.

Rabbits were adapted to restraint in attenuation box one week before the beginning of the conditioning procedure. The box restricted the body rotation. A rabbit in a box was trained in a sound-attenuated chamber. A holder common for the air puff nozzle and for the photoelectric transducer was mounted on the rabbit's headpiece with a screw. The rabbits were trained on simple delay classical conditioning (Berger and Thompson 1978), pairing of a tone (CS) with a co-terminating air puff (US) on each trial, directed at the left eye. The training was given in 120 consecutive trials each day, with an intertrial interval averaged 22 s. Eyelid responses initiated in the time interval between CS and US onsets, exceeded 1 mm in amplitude, were classified as conditioned responses (CRs) and were calculated as a percentage of all 120 paired trials applied during one-day session. The rabbits typically learned to a maximal level of learning of 80-90 % in 2-3 days, but were overtrained until 5th days to strengthen the memory trace. Five days' extinction procedure was applied, when phonopneumatic stimulator generated only 120 tone stimuli (CS). Eyelid responses elicited by CS alone were classified as CRs.

Microdialysis procedure. Microdialysis probes (CMA/Microdialysis, Sweden, Cat.No. 8309504) were implanted unilaterally into the hippocampus or the caudate nucleus. The microdialysis membranes were 4 mm long, with an outer diameter of 0.5 mm and a 20,000 molecular weight cut off. The last parameter determines the molecular-weight limit of the compounds passing dialysis membrane pores. The outlet tubing was cut shorter to a length of 100 mm, that is 1/3 of the inlet tubing length. On the day of implantation the rabbit was put into an attenuation box and a 20 % solution of mannitol was infused intravenously at the amount of 600 mg per kg. b.w. Then, the stilette was removed from the guide cannula. The microdialysis probe filled and continuously perfused with degassed 0.9% NaCl solution and ste-

Table 1
The course of proceeding during microdialysis of the rabbit hippocampus. In the case of the caudate nucleus dialysis the experiments were performed in the same way except the NaCl-4 and OXT 50.0 group

day of experiment	procedure (group of variables)
1 – 5	acquisition
6 – 10	extinction
11 – 15	acquisition
16 – 20	extinction
21	implantation of the microdialysis probe
22 – 26	acquisition and dialysis of the hippocampus with 0.9% NaCl solution
27 – 31	extinction and dialysis of the hippocampus with 0.9% NaCl solution (control E), Fig. 2
32 – 36	acquisition and dialysis of the hippocampus with 0.9% NaCl solution (control A), Fig.3
37 – 41	extinction and dialysis of the hippocampus with OXT in concentration of 0.05 μg/ml (OXT 0.05), Fig. 2
42 – 46	acquisition and dialysis of the hippocampus with 0.9% NaCl solution (NaCl-1), Fig. 3
47 – 51	extinction and dialysis of the hippocampus with OXT in concentration of 0.5 μg/ml (OXT 0.5), Fig. 2
52 – 56	acquisition and dialysis of the hippocampus with 0.9% NaCl solution (NaCl-2), Fig. 3
57 – 61	extinction and dialysis of the hippocampus with OXT in concentration of 5.0 μg/ml (OXT 5.0), Fig. 2
62 – 66	acquisition and dialysis of the hippocampus with 0.9% NaCl solution (NaCl-3), Fig. 3
67 – 71	extinction and dialysis of the hippocampus with OXT in concentration of 50.0 μg/ml (OXT 50.0), Fig. 2
72 – 76	acquisition and dialysis of the hippocampus with 0.9% NaCl solution (NaCl-4), Fig. 3

rilized with 70 % ethanol, was very slowly inserted into the guide cannula under the operation stereomicroscope and tentative microdialysis was performed for 10 minutes. The perfusion was then performed either with 0.9 % NaCl or with OXT solution (see Experimental protocol and Table 1) at a rate of 1 μl/min using 1 ml syringe and a syringe pump for simultaneous multiple infusions (model SP 220i, World Precision Instruments).

Experimental protocol. Rabbits with implanted headpieces underwent 5 days of acquisition and 5 days of extinction training repeated two times. After this preliminary training the run of both was regular and stable to the consecutive comparative studies. Then the probe was implanted into the chosen structure and the control microdialysis was performed with 0.9 % NaCl solution simultaneously with renewed acquisition (control A) and then extinction (control E) procedure. After the control acquisition the extinction procedure was done simultaneously with microdialysis of the hippocampus with OXT solution at concentrations of 0.05; 0.5; 5.0 and 50.0 μg/ml (OXT 0.05; OXT 0.5; OXT 5.0 and OXT 50.0 groups of variables). Taking into consideration the time and rate of microdialysis and the *in vivo* delivery of the probe determined by Engelmann et al. (1992) for AVP as 0.5%, about 0.01; 0.1; 1.0 and 10.0 ng OXT could deliver from the probe into the brain tissue. After each extinction procedure with OXT treatment, acquisition simultaneous with 0.9 % NaCl dialysis of the hippocampus was performed (NaCl-1; NaCl-2, NaCl-3 and NaCl-4 groups of variables) to obtain so called after-OXT acquisition groups of variables. In the case of caudate nucleus dialysis experiments were performed in the same way except the OXT 50.0 and NaCl-4 groups of variables. Table 1 summarizes the course of proceeding in the case of hippocampus dialysis. Hippocampus was dialyzed in 11 and caudate nucleus in 12 conscious rabbits.

Probes position in the brain structures was marked with 10 % Ianus Green microdialysis after the experiments and was histologically verified in sections of the brain fixed with 10% formalin solution and frozen.

Data analysis and statistical evaluation. Values of percentage responses were transformed according to the formula: 2 x arcsin $\sqrt{p}$. Statistical significance was determined by two independent (for hippocampal and caudal experiments), three-way ANOVA involving the factors of group, stage of training (acquisition/extinction) and day of training (1-5), with repeated measures on the two last factors. Five groups of data were analysed when OXT was dialyzed into the hippocampus (control + four OXT concentrations), and four groups during caudate nu-

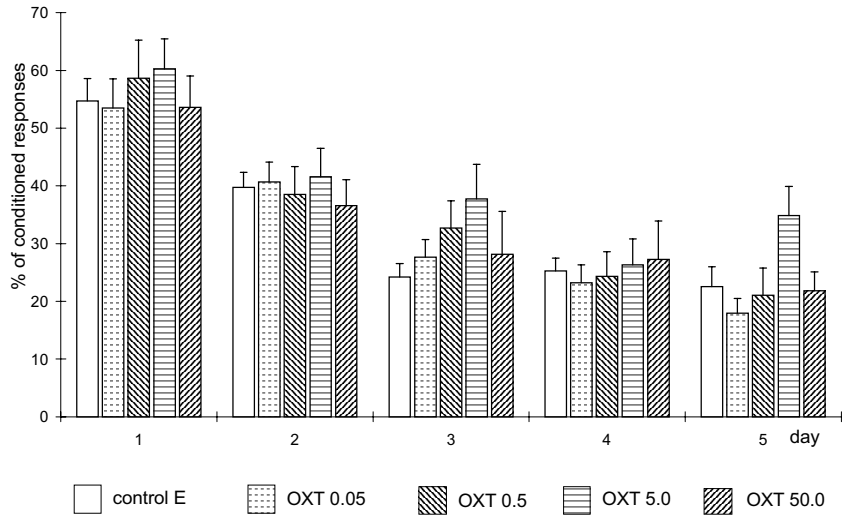

Fig 2 The course of the extinction of the conditioned eyelid reflex in rabbit during five days of training and OXT dialysis into the hippocampus (means ± SE). The tendency to impairment of forgetting is visible.

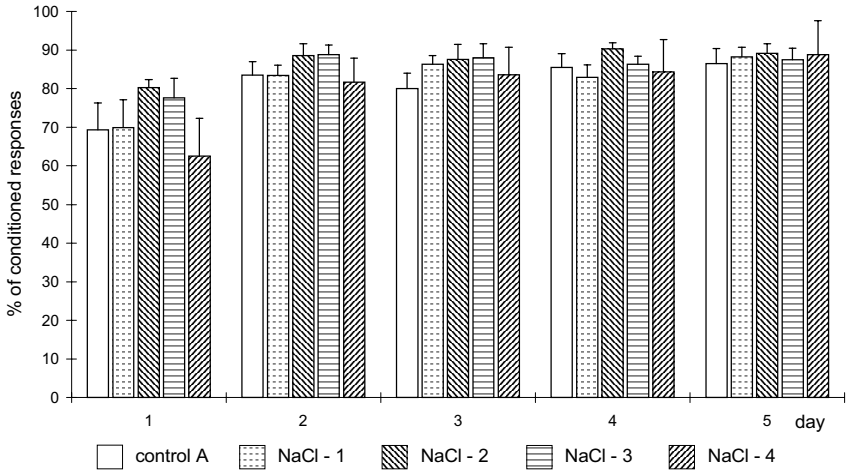

Fig 3 The course of the acquisition of the conditioned eyelid reflex during five days of training in rabbit pre-dialyzed into the hippocampus with OXT (means ± SE).

cleus dialysis (control + three OXT concentrations) while acquisition or extinction training. Differences were considered significant if $p<0.05$.

Results

Influence of oxytocin dialyzed into the hippocampus on the acquisition and extinction. The mean percentage of responses (±SE) on the test day of extinction is illustrated for each group in Figure 2 and on the day of acquisition in Figure 3. ANOVA revealed a statistically significant difference in day performance ($F_{4,120} = 3.5$), $P = 0.01$, stage of training of conditioned eyelid reflex ($F_{1,30} = 429.2$), $P = 0.000$ and interaction of both effects ($F_{4,120} = 51.1$), $P = 0.000$. The main effect of group was insignificant ($F_{4,30} = 0.8$), $P = 0.537$ like group x day x stage of training interaction ($F_{16,120} = 0.9$), $P = 0.595$. It indicates that the NaCl control and OXT groups (extinction) and after OXT groups (acquisi-

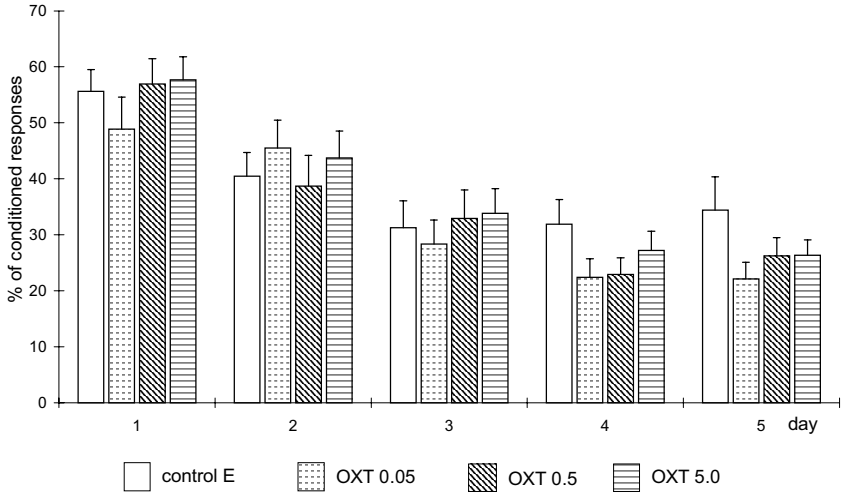

Fig 4 The course of the extinction of the conditioned eyelid reflex in rabbit during five days of training and OXT dialysis into the caudate nucleus (means ± SE). Some symptoms of facilitation of forgetting are visible on the 4th and 5th day of the extinction.

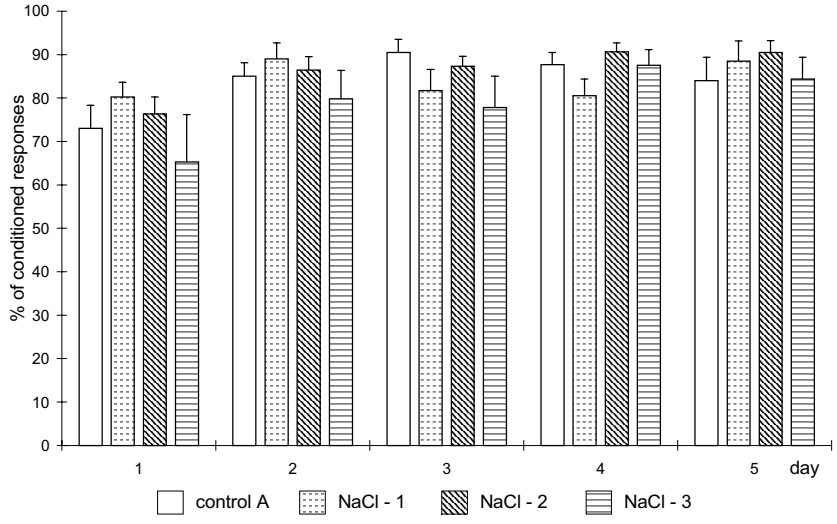

Fig 5 The course of the acquisition of the conditioned eyelid reflex during five days of training in rabbit pre-dialyzed into the caudate nucleus (means ± SE).

tion) of animals displayed similar performance during the extinction and acquisition training. Figure 2 shows that OXT treatment of the hippocampus during the extinction of the learned skill only somewhat insignificantly changed its course especially on the 3rd and 5th day of extinction when concentration of 5.0 μg/ml was applied. Figure 3 shows some small tendency to improving learning. Thus it may be stated that OXT dialyzed through the hippocampus during the extinction training did not change the process of learning and forgetting of the skill in a significant manner.

Influence of OXT dialyzed into the caudate nucleus on the acquisition and extinction. Figure 4 presents the mean percentage of responses (± SE) on the test day of extinction and Figure 5 shows the

data obtained on the acquisition days in rabbits dialyzed with OXT into the caudate nucleus. ANOVA showed a significant effect of the day factor ($F_{4,116}$ = 7.20), P = 0.000, stage of training ($F_{1,29}$ = 291.35), P = 0.000 and day x stage of training interaction ($F_{4,116}$ = 40.07), P = 0.000. Effect of group factor was not significant ($F_{3,29}$ = 0.42), P = 0.74 as well as group x day x stage of training interaction ($F_{12,116}$ = 1.52), P = 0.13. As shown above in Figure 4, only insignificant tendency to acceleration of the extinction was observed which means the facilitation of the forgetting process. This effect is the most visible on the 4th and the 5th day of extinction. As shown above in Figure 5 either some insignificant tendency to improvement or to impairment of learning was observed. Thus it may be stated that OXT dialyzed into the caudate nucleus during the extinction training did not change the process of learning and forgetting of the new association.

Discussion

The data obtained in the present paper point out that OXT dialyzed into the hippocampus or into the caudate nucleus did not change significantly the course of memory processes essential for conditioning of the eyelid reflex in rabbits. In contrast, AVP impaired forgetting when dialyzed into both structures in our previous experiments, but the effect in the hippocampus was greater and long lasting (Orlowska-Majdak et al. 2001 b). However, TRH dialyzed into the hippocampus not only restrained the process of forgetting of the learned task but also improved the process of succeeding learning (Kolodziejski et al. 2001).

The results of intrahippocampally applied OXT in rabbits obtained in the present paper are partially consistent with the results observed by Ibragimov (1990) in rats. In his experiment OXT weakened the formation of active avoidance behaviour during the acquisition training but did not change the course of extinction during the six day training. In our experiments OXT neither changed the course of acquisition nor extinction during the five day training. Differences between the results quoted above and our observations may result from other species used in the experiments (rat vs. rabbit), other experimental models of learning (active avoidance behaviour vs. conditioned eyelid reflex) and the ways of administration of the peptide into the brain structure (infusion vs. microdialysis).

In the present experiment the peptide was administered repeatedly, during extinction, by a microdialysis probe. It is generally held that microdialysis causes minute tissue trauma compared with other methods using direct tissue penetration, i.e. direct intracerebral injection (Benveniste 1989). Moreover, in the present experiment OXT was dialyzed into the structure only during the extinction, while in the study by Ibragimov (1990) it was 60 min before the acquisition or extinction. In our experimental model such protocol was impossible.

In this study the control and OXT evoked responses were observed in the same rabbits in which microdialysis probe tips were positioned exactly at the same point of the brain structure (see Table 1). Therefore the peptide dialyzed into the brain structure acted always at the same area of the structure as the control solution did. Some inconvenience of such experimental protocol was multiple administrations of OXT into both brain structures. Such repetitive administration of OXT produced a desensitisation of the OXT receptor on hypothalamic cultured astrocytes (Di Scala-Guenot et al. 1994) and could desensitize the OXT receptors on hippocampal and caudal neurons in our experiments.

There are more other conflicting reports on OXT participation in memory processes (see Introduction). When OXT was administered peripherally in rats in initial experiments of De Wied and Gispen (1977) it mimicked the effect of AVP on avoidance extinction that is it increased resistance to extinction. This result was in accordance with a tendency observed in the present experiments when OXT was dialyzed into the hippocampus.

Neuropeptides AVP and OXT act peripherally and centrally through their receptors. Cerebral OXT receptors discriminate rather poorly between AVP, OXT and vasotocin (De Wied et al. 1991). Moreover, conflicting data were published on the nature and function of OXT receptor. Although most brain areas which contain OXT binding sites have been shown to express OXT mRNA using DNA probes derived from the uterine OXT receptor, in the hippocampus and in the amygdala the antibodies raised against rat OXT receptor sequences failed to identify OXT receptor immunoreactivity (Verbalis 1999).

Consequently, the possibility of a second OXT receptor or OXT receptor subtype persists (Verbalis 1999). Characteristics of this alleged receptor are unknown. Moreover OXT-binding sites have been described in both neuron-enriched cultures as well as in pure astrocyte cultures (Di Scala-Guenot and Strosser 1992), so a possibility exists that OXT could additionally act by modulating the efficiency of the synaptic transmission. This may be the reason of cited above conflicting results of OXT action on animal behaviour.

Caudate nucleus was chosen as the reference structure for hippocampus for these OXT experiments because OXT receptors were revealed in this structure (Condes-Lara et al. 1994; Tribollet et al. 1988) and the contents of endogenous OXT in the hippocampus and in the caudate nucleus in the rat were revealed as similar, that is 1.05 pg OXT/mg protein and 1.71 pg OXT/mg protein, respectively (Hawthorn et al. 1984). But none significant effect of OXT dialysis through the caudate nucleus was observed in present experiments, similarly as during hippocampal dialysis.

The possible involvement of OXT in memory processes in the eyelid conditioning in rabbit needs to be further studied. Measurement of the latency of the reflex perhaps could be better than the percentage of conditioned responses counted in the present paper to distinguish and demonstrate OXT action in eyelid reflex conditioning. Moreover, the trace paradigm could be more useful than delay paradigm to study the role of OXT in hippocampus in eyelid reflex conditioning. It is believed that the hippocampus is necessary for acquisition of the trace but not the delay classical conditioning response (Solomon et al.1986), used in our experiments. In the delay paradigm, rabbits were given an auditory conditioned stimulus that coterminated with an airpuff to the eye. The trace paradigm is similar to the delay paradigm, except that some interval separates the offset of the auditory stimulus from the onset of the airpuff.

Acknowledgements

This research was supported by Medical University of Lodz, fund nr 503-104-4 and partially by the European Community (BIOMED-1, Associated contract ERBBMHICT 921193). The authors wish to thank Mrs Krystyna Sadzinska and Mrs Anna Kliszko for their help with surgery, animals care and for technical assistance during the experiments, and Mr Krzysztof Majdak for drawing figures.

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