Arginine Vasopressin Fragment AVP_{4-9} Facilitates Induction of Long-Term Potentiation in the Hippocampus

A. N. Chepkova, N. A. Kapai, and V. G. Skrebitskii

Translated from *Byulleten' Eksperimental'noi Biologii I Meditsiny*, Vol. 131, No. 2, pp. 167-169, February 2000
Original article submitted December 30, 2000

Long-term potentiation of CA1 field potentials was induced by weak tetanic orthodromic stimulation of the Schaffer collateral/commissural fibers in isolated hippocampal slices perfused with a medium containing arginine vasopressin fragment AVP_{4-9} in micromolar concentrations. It is hypothesized that AVP_{4-9} affects induction of long-term potentiation at the intracellular level.

Key words: *neuropeptides*; *arginine vasopressin fragment AVP_{4-9}*; *hippocampus*; *long-term potentiation*

Arginine vasopressin (AVP), a neuropeptide involved in endocrine regulation of the water-electrolyte balance and blood pressure, also plays a role in the regulation of some central nervous functions including memory and learning [7]. It was established that memory-related effects of AVP are realized in the limbic system, predominantly in the hippocampus [10]. These effects are considered to be mediated by the C-terminal fragments of the peptide, which are formed during AVP metabolism in the brain [12]. Different experimental models of learning (including passive avoidance and maze tests) revealed that the main AVP metabolite [$pGlu^4$-Cyt^6] AVP_{4-9}, which has no hormonal activity, exhibited a more pronounced and selective effect on memory compared to AVP [5,8,9,14]. Despite considerable attention focused at this peptide, the mechanisms of its memory-related effects are not clearly understood.

At the cellular level, memory is associated with changes in the efficacy of synaptic transmission. It can be assumed that the improvement of memory function by vasopressin-like peptides is related to their influence on long-term potentiation in the hippocampus, which is considered as a neurophysiological model of memory [3]. We studied the effect of AVP_{4-9}, the main AVP metabolite, on long-term potentiation (LTP) in the Schaffer collateral—pyramidal CA1 cells system (SC—CA1).

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 100-180 g. Isolated hippocampal slices were placed into the recording chamber and perfused with modified Ringer solution containing (in mM): 124 NaCl, 3 KCl, 2.5 $CaCl_2$, 2.5 $MgSO_4$, 1.25 Na_2HPO_4, 26 $NaHCO_3$, and 10 D-glucose, continuously aerated with carbogen (95% O_2+ 5% CO_2) at 29-30°C. Electrical activity was recorded 1.5-2 h after preparation of hippocampal slices. The hippocampal radial layer was stimulated with single 0.1-msec square pulses, delivered at a frequency of $^1/_{15}$ sec^{-1} via bipolar electrodes filled with the perfusate. Evoked field potentials were recorded in the pyramidal CA1 layer using a glass microelectrode (2-5 mΩ) filled with 1.5 M NaCl. The stimulus strength corresponded to that required to produce responses of as high peak amplitude as 40 to 50% of maximum population spike of pyramidal neurons (pop-spike, PS). Potentiation of PS was produced by high frequency stimulation (HFS, 100 Hz) of presynaptic inputs with pulses of the same current strength and applied via the same stimulating electrodes. Only one HFS was performed in each slice. Fifteen minutes

Institute of Brain Research, Russian Academy of Medical Sciences, Moscow. ***Address for correspondence:*** chepkova@cc.nifhi.fc.ru. Chepkova A. N.

0007-4888/02/1312-0136$25.00

before HFS the perfusion system was switched to a reservoir containing standard saline (control) or solution containing AVP_{4-9} (Sigma) in concentrations of 0.01, 0.1, 1.0, and 5.0 μM. Normal perfusion was resumed 5 min after the end of HFS. Aliquots of the basic solution of AVP_{4-9} dissolved in deionized water were stored in a refrigerator and adjusted to a required concentration immediately before the experiments.

Responses of pyramidal neuron during application of AVP_{4-9} and after HFS were evaluated by deviations of PS amplitude from its mean value determined for a 15-30-min period of background activity (before perfusion with test medium). The data were processed statistically using nonparametric Mann—Whitney's *U* test. All values are given as mean±SEM.

RESULTS

In series I we studied the effect AVP_{4-9} on LPT induced by short-term weak HFS (30 pulses, 100 Hz) of the radial layer. In the control, this stimulation induced only a slight potentiation of the field response. PS amplitude increased immediately after HFS, but then rapidly decreased, and 15 to 30 min after stimulation returned to the baseline (Fig. 1, *a*).

After AVP_{4-9} administration, weak stimulation induced long-term (persisted for 1 h) potentiation of responses (Fig. 1, *a*). The development of LTP nonlinearly depended on AVP_{4-9} concentration: it was maximum (100%) in the presence of 1 μM of AVP_{4-9} and decreased at higher (5 μM) and lower (0.1 μM) concentrations of the peptide, but still remained above the control level (Fig. 1, *b*). In this of concentration range, the test peptide had no effect on PS amplitude.

In series II we studied the effect of 1 μM AVP_{4-9} (optimal dose) on LPT induction by standard HFS (100 pulses, 100 Hz) of radial layer, which induced LTP of the focal response in all control preparations (Fig. 2). Under these conditions, pretreatment with AVP_{4-9} had no effect on LTP induction, but slightly decreased its mean amplitude for 1 h of observation from 144.1±9.2% (n=8, control) to 135.3±10.2% (n=4, p<0.05).

Thus, the modulating effect of AVP_{4-9} on the development LTP in the hippocampus depended on the intensity of HFS. AVP_{4-9} facilitated induction of LTP after weak stimulation and did not significantly change it under conditions of more potent presynaptic activation. It should be noted that the mean LTP amplitude induced by weak HFS after application of 1 μM AVP_{4-9} was 160.2±13.7%, *i.e.* significantly surpassed the level of LTP after standard HFS observed in the control (p<0.05). These findings together with previous observation that LTP induced by standard HFS after application of AVP_{4-9} is decreased suggest that AVP_{4-9} not only facilitates LTP induction, but also modulates its amplitude depending on the intensity of presynaptic inflow.

Our findings agree with previous studies demonstrating facilitation [11] and prolongation [2] of LTP in the SC—CA1 pathway produced by AVP in the presence of vasopressin and vasopressin-like peptides. It was also shown that desglycinamide-vasopressin and AVP_{4-8}, desglycinamide AVP_{4-9} derivative, increased LTP ampli-

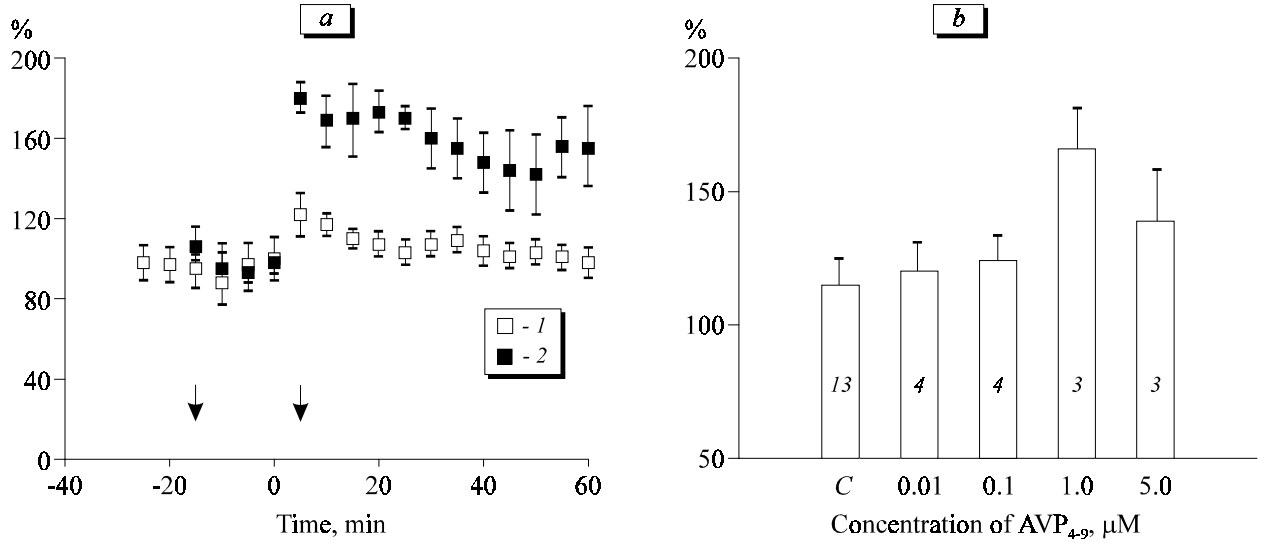

Fig. 1. The effect of AVP_{4-9} on long-term potentiation of CA1 field potentials in rat hippocampal slices after weak high-frequency stimulation (HFS). *a*) Changes in amplitude of population spike. Here and on Fig. 2: time 0 corresponds to the start of HFS, application of AVP_{4-9} is indicated by arrows. Mean amplitude of the response in the control (*1*) and after application of AVP_{4-9} (*2*). Mean value of potentiation (*b*) from 0 to 40 minutes after HFS in control (*C*) and after perfusion with AVP_{4-9} in different concentrations. Figures in bars show the number of experiments in each series.

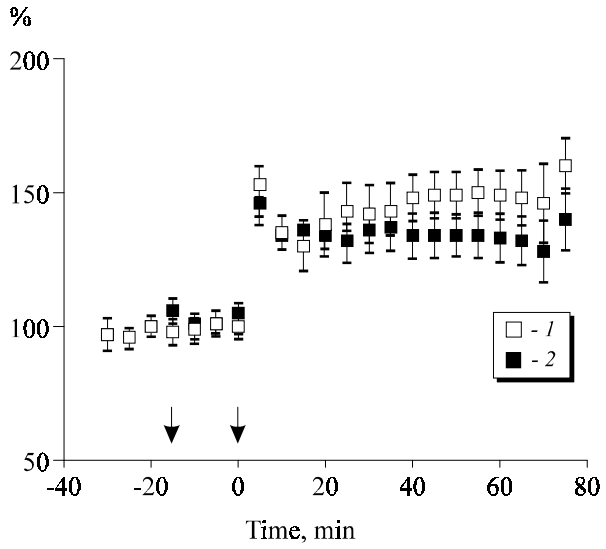

Fig. 2. Long-term potentiation of CA1 field potentials in rat hippocampal slices after standard high-frequency stimulation (HFS). Changes in pop-spike amplitude.

tude in this synaptic system [1,13]. Moreover, AVP and fragment AVP_{4-8} can induce long-term facilitation of synaptic transmission in the SC—CA1 system [6,13], which differs by its pharmacological properties from LTP induced by electrical stimulation [6].

We found no published data on electrophysiological effects of AVP_{4-9}. According to biochemical studies, AVP_{4-9} stimulates hydrolysis of inositol-phospholipides via activation of hippocampal V_1-receptors, enhance Ca^{2+} entry into cells, and increase intracellular Ca^{2+} concentration [4]. Another way of induction of LTP in the SC—CA1 pathway is associated with the rise of intracellular Ca^{2+} due to activation of the NMDA-subtype glutamate receptor complex and voltage-dependent Ca^{2+}-channels [3]. It can be hypothesized that AVP_{4-9} facilitates induction of LTP and increases its amplitude under conditions of weak stimulation of the glutamatergic input due to activation of intracellular calcium signaling system.

The study was supported by the Russian Foundation of Fundamental Researches (grants No. 98-04-48311 and No. 00-15-97923).

REFERENCES

1. I. E. Kudriashov and E. M. Ivanova, *Zh. Vyssh. Nervn. Deyat*, **45**, No. 3, 589-592 (1995).
2. A. N. Chepkova, *Ibid.*, **31**, No. 2, 427-430 (1981).
3. T. V. P. Bliss and G. L. Collingridge, *Nature*, **361**, 31-39 (1993).
4. R. D. Brinton, T. M. Gonzalez, and W. S. Cheung, *Brain Res.*, **661**, 274-282 (1994).
5. J. P. H. Burbach, G. L. Kovacs, D. De Wied, *et al.*, *Science*, **221**, 1310-1314 (1983).
6. A. N. Chepkova, P. French, and D. De Wied, *et al.*, *Brain Res.*, **701**, 255-266 (1995).
7. D. De Wied, *Neurobiology of Learning and Memory*, Eds. G. Lynch, *et al.*, 289-312, New York (1984).
8. A. Dietrich, J. D. Allen, *Behav. Brain Res.*, **87**, No. 2, 195-200 (1997).
9. Fujiwara M, Ohgami Y, Inada K, Iwasaki K, *Ibid*, **83**, No. 1-2, 91-96 (1997).
10. G. L. Kovacs, H. D. Veldhuid, D. H. G. Versteeg, and D. De Wied, *Brain Res.*, **380**, 325-330 (1986).
11. N. Miura, S. Shibata, and S. Watanabe, *Behav. Brain Res.*, **83**, No. 1-2, 213-216 (1997).
12. L. G. Reijmers, J. M. van Ree, B. M. Spruijt, *et al.*, *Prog. Brain Res.*, **119**, 523-535 (1998).
13. X.-W. Rong, X.-F. Chen, Yu.-C. Du, *Neuroreport*, **4**, 1135-1138 (1993).
14. S. Tanabe, Y. Shishido, M. Furushiro, *et al.*, *Pharmacol. Biochem. Behav.*, **57**, No. 1-2, 251-256 (1997).