Inhibition by [Arg^8]-Vasopressin of Long Term Potentiation in Guinea Pig Hippocampal Slice

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ABSTRACT—We examined the effects of [Arg^8]-vasopressin (AVP) on long term potentiation (LTP) of the field excitatory postsynaptic potentials at CA1 and CA3 synapses in adult guinea pig hippocampal slices. AVP (10 nM) depressed the magnitude of LTP without any effects on basal responses at both synaptic pathways. The depressive effect by AVP at CA1 synapses appears to be receptor-mediated since it was inhibited by an AVP V1-receptor antagonist, [Pmp^1,Tyr(Me)^2]-AVP. From these results, AVP may play an inhibitory role on the induction of LTP via V1 receptors in the guinea pig hippocampus.

Keywords: [Arg^8]-vasopressin, Long term potentiation, Hippocampus

Several lines of evidence have indicated that [Arg^8]-vasopressin (AVP) behaviorally modulates learning and memory in various experimental models. Although the action of AVP on memory has been predominantly shown to be facilitatory (1), the centrally active metabolite of vasopressin can interfere with the acquisition of a cognitive learning task when administered concomitantly with training (2). In electrophysiological studies, both excitatory and inhibitory actions of AVP have been observed in isolated slice preparations of the rat hippocampus (3, 4). The present experiments were undertaken to explore the effects of AVP on long term potentiation (LTP) of the field excitatory postsynaptic potentials (EPSPs) at hippocampal CA1 and CA3 synapses, which is widely accepted as a cellular model of plasticity. The effect of a V1-receptor-subtype antagonist on LTP was also examined.

Slice preparation and electrophysiological recording were performed as previously described (5). Briefly, transverse slices, 500-μm-thick, were obtained from the ventral hippocampus of male guinea pigs (200–300 g). When a recording was made, a slice was continuously perfused with artificial cerebrospinal fluid (aCSF) containing 124 mM NaCl, 2 mM KCl, 1.24 mM KH_2PO_4, 3 mM $MgSO_4$, 3 mM $CaCl_2$, 26 mM $NaHCO_3$, 10 mM glucose, and bubbled with 95% O_2–5% CO_2. Responses at CA1 and CA3 synapses were evoked by electric stimuli of 0.1-msec duration applied at a frequency of 0.2 Hz with a strength that was 50%–60% of the maximum response to the Schaffer collateral/commissural and the mossy fibers, respectively. Field EPSPs were recorded from the stratum radiatum at CA1 (5) or the stratum lucidum at CA3 region (6), using a glass micropipette filled with 0.9% NaCl. Ten successive field EPSPs were recorded and averaged every 5 min. After a stable response was observed for 30 min, tetanic stimulation at 33 Hz for 5 sec was applied to induce LTP. The magnitude of LTP is expressed as the percent change in the amplitude of field EPSP compared with the average one measured 3–13 min before tetanic stimulation. AVP and [1-(β-mercapto-β,β-cyclopentamethylene propionic acid), 2-(*O*-methyl)-tyrosine]-Arg^8-vasopressin ([Pmp^1,Tyr(Me)^2]-AVP) were dissolved in distilled water for the stock solutions, which were then diluted in aCSF for application. Both peptides were purchased from Peptide Institute, Inc., Osaka. The peptides were perfused onto the slice for 20 min from 15 min before the tetanic stimulation.

Brief tetanic stimulation of Schaffer-collateral/commissural or mossy fiber pathway evoked a 40%–50% increase in the magnitude of field EPSP without any change in latency and seizure discharge as compared to those of control slices. Sustained potentiation was observed for more than 60 min after tetanic stimulation and recognized as LTP. A bath application of AVP (10 nM) did not affect the latency and pattern of field EPSPs before tetanic stimulation at CA1, but it did inhibit the induction of LTP (Fig. 1a). The effect of AVP on the LTP at CA1 synapses was concentration-dependent in a

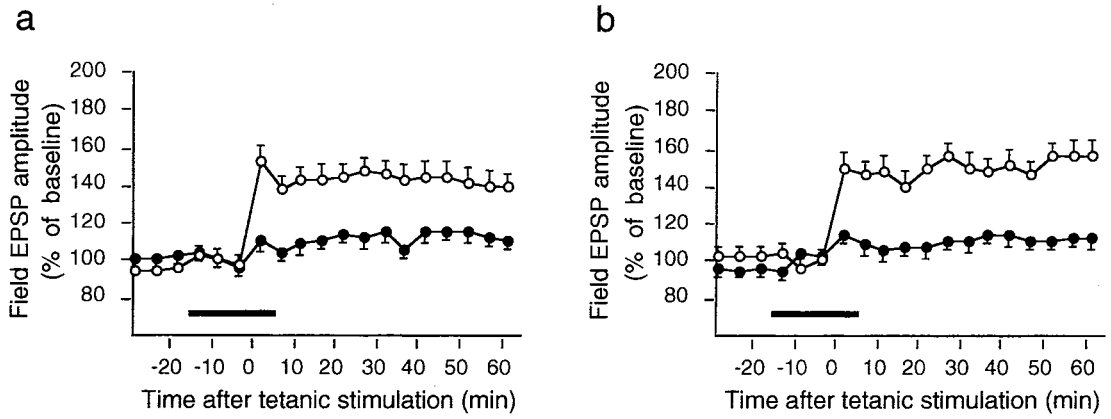

Fig. 1. Effects of AVP on LTP at Schaffer collateral-CA1 (a) and mossy fiber-CA3 (b) synapses. Normalized field EPSP amplitude is plotted against time after tetanic stimulation. ○, control (a, n=6; b, n=8); ●, AVP, 10 nM (a, n=6; b, n=5). AVP was applied during the time indicated by the solid bar.

range from 0.1 to 10 nM (Fig. 2). The average increase in the amplitude of field EPSPs from 2 min to 62 min after tetanic stimulation was significantly inhibited by AVP at 1 nM (17.3±7.6% increase) and 10 nM (11.5±2.4% increase), as compared to the control (44.1±7.7% increase). The effect of a higher concentration (100 nM) was also suppressive; however, the difference from the control was smaller than that at 10 nM. [Pmp^1,$Tyr(Me)^2$]-AVP was reported to be a selective antagonist for AVP V1 receptor, which is a major subtype of AVP receptors in the CNS (7). When the effect of the antagonist itself (100 nM) was evaluated at CA1 synapses, a slight but not significant decrease in the amplitude of LTP was observed. When the AVP antagonist was co-applied with 10 nM AVP, which showed a potent inhibitory effect on LTP, the V1 antagonist decreased the suppressive effect of AVP in a concentration-dependent manner at 10−1000 nM (Fig. 3). At CA3 synapses, AVP (10 nM) also showed suppressive effects on tetanus-induced LTP without affecting the latency and pattern of field EPSPs before tetanic stimulation (Fig. 1b).

The present results clearly indicate that AVP suppresses LTP without affecting the basal field EPSPs at both Schaffer collateral-CA1 and mossy fiber-CA3 synapses,

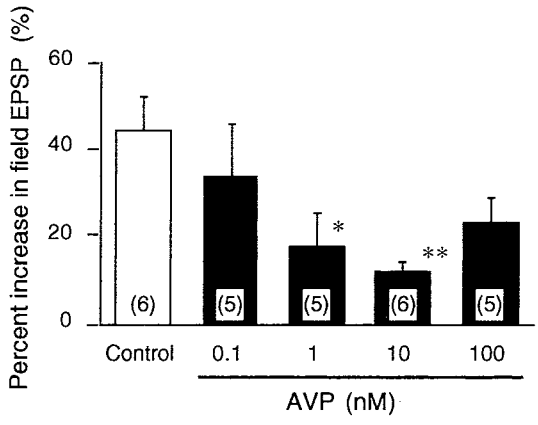

Fig. 2. Concentration-dependent effects of AVP on LTP at Schaffer collateral-CA1 synapses. AVP was perfused from 15 min before tetanic stimulation for 20 min. Percent changes in the magnitude of field EPSPs are shown as the mean±S.E.M. Comparisons versus control were made by the Welch *t*-test. *P<0.05, **P<0.01. The numbers in parentheses indicate the number of experiments.

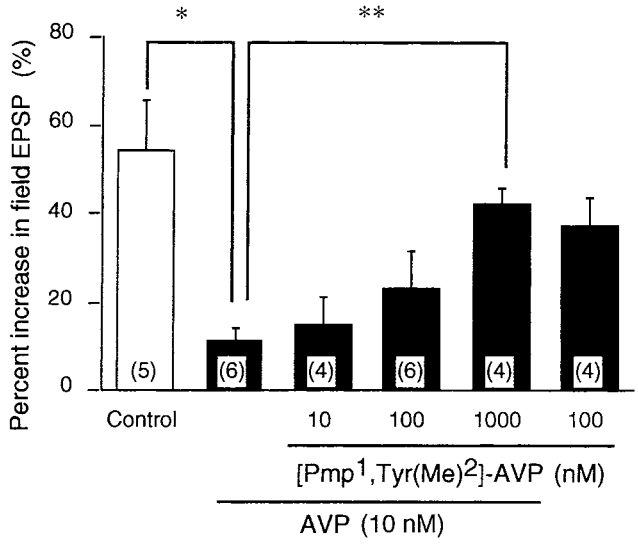

Fig. 3. Antagonism of AVP effect on LTP at Schaffer collateral-CA1 synapses by V1 antagonist. Combination of AVP and antagonist were perfused from 15 min before tetanic stimulation for 20 min. Percent changes in the magnitude of field EPSPs are shown as the mean±S.E.M. Comparisons versus AVP at 10 nM alone were made by the Welch *t*-test. *P<0.05, **P<0.01. The numbers in parentheses indicate the number of experiments.

suggesting that AVP specifically modulates the induction of LTP in guinea pig hippocampus. Blockade by the V1 antagonist of the suppressive effect of AVP reveals that V1 receptors dominantly participate in the effect of AVP on LTP at hippocampal CA1. The fact that [Pmp[1],Tyr(Me)[2]]-AVP itself exerted a slight suppression of LTP may reflect that the V1 antagonist intrinsically has a partial agonistic property, like another peptide V1 antagonist does (8).

Our results seem opposite to a recent report in which AVP (10 nM) coupled with tetanus caused an augmentation of field EPSP at CA1 synapses in rat hippocampal slices (9). Since the effective concentration range of AVP or the experimental paradigm is similar, this discrepancy may result from species differences in the action of AVP. However, in our experiments, inhibitory effects of AVP were observed in both Schaffer collateral and mossy fiber synapses where those LTPs are caused by different mechanisms (10). Therefore, the suppressive effect of AVP may be mediated by a common mechanism, such as AVP stimulating inhibitory interneurons (4, 11) that are depressed after tetanic stimulation (12).

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