Cholecystokinin and response modifications in hippocampal field CA1

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This study indicates that cholecystokinin (CCK-8S) and high-frequency afferent stimulation (HFS) modify neuronal responses to stimulation of the perforant pathway in hippocampal field CA1. HFS, previously neutral with regard to modifications, induced depression of both field evoked action potentials (EAPs) and field excitatory postsynaptic potentials (EPSPs) in the presence of 500 nM CCK-8S. However, in the presence of 1 μ M CCK-8S, HFS induced a potentiation of both field evoked responses. With intermediate concentrations of CCK-8S, HFS was indifferent to potentiation or depression: 750 nM CCK-8S was not associated with modifications, whereas only potentiation of EAPs occurred with 900 nM CCK-8S. The mechanism underlying HFS/CCK-8S-induced LTP or LTD may involve reduction of γ -aminobutyric acid (GABA) release. LTP and LTD may underlie certain forms of memory, and this study implicates hippocampal CCK-8S/GABAergic pathways in their induction.

The neuronal substrate of memory in the mammalian brain may involve modifications that persist well beyond their period of activation. Long-term potentiation (LTP) or long-term depression (LTD) are examples of such modifications (Bliss & Lomo, 1973; Levy & Steward, 1979). In the hippocampal formation, support for a presumptive relationship between long-lasting neuronal modifications and memory is provided by the finding that aphosphonopentanoic acid (APV), an *N*-methyl-D-aspartate (NMDA) receptor antagonist, which blocks induction of long-lasting potentiation or depression (Dahl & Sarvey, 1990; Harris, Ganong, & Cotman, 1984), also prevents acquisition in behavioral tasks (Morris, 1989; Morris, Anderson, Lynch, & Baudry, 1986).

LTP and LTD can be induced by high-frequency stimulation (HFS) of afferent pathways (Bliss & Lomo, 1973; Levy & Steward, 1979). Induction may involve an associative interaction *within* an afferent pathway (McNaughton, Douglas, & Goddard, 1978), but there is ample evidence implicating interactions *between* pathways as well. In addition to excitatory neurotransmission, induction of LTP in the hippocampal formation involves modulation of GABAergic inhibitory neurotransmission (Wigstrom & Gustafsson, 1983); neuromodulators such as norepinephrine (NE; Hopkins & Johnston, 1984); or the neuropeptides somatostatin (Scharfman, 1993) or cholecystokinin (CCK-8S; Dahl, Bennett, & LeCompte, 1992; Kawasaki & Yasui, 1992). In addition to effects on the induction of LTP, CCK-8S also facilitates acquisition

in behavioral tasks (Fekete et al., 1984; Flood, Smith, & Morely, 1987; Telegdy, Kadar, & Fekete, 1985).

Differentiation of HFS-induced long-lasting potentiation or depression correlates with postsynaptic membrane potential (Artola, Broecker, & Singer, 1990; Xie, Berger, & Barrionuevo, 1992). If CCK-8S modulates GABA release in hippocampal field CA1, as was suggested by Rich-Bennett, Dahl, and LeCompte (1993) for the dentate gyrus, then CCK-8S may also modulate induction of potentiation or depression. In the present work, hippocampal slices were perfused with several concentrations of CCK-8S in conjunction with HFS to determine whether CCK-8S provides an additional factor in the differential induction of LTP or LTD.

METHOD

Preparation

Middorsal hippocampal slices (400 μ m) were cut from the brains of male rats (Sprague-Dawley, 100–125 g) using a McIlwain Tissue Chopper. Slices were placed on a nylon net in a modified Andersen-type chamber at the interface between circulating artificial cerebrospinal fluid (ACSF) and a warmed, humidified atmosphere consisting of 95% O₂/5% CO₂. Buffered ACSF (pH = 7.2) has the following composition (in mM): NaCl 125, KCl 3, MgSO₄ 1.3, CaCl₂ 2.4, NaHCO₃ 26, NaH₂PO₄ 1.25, and glucose 10. Stabilization of slices occurred over a period of 1 h with continuous ACSF perfusion at a flow rate of 3 ml/min. The temperature of the chamber was maintained 31°C.

Electrophysiological Techniques

Stimulation electrodes consisted of Teflon-coated platinum-iridium wires (ca. 80 μ m diam) mounted in a drawn glass capillary. A stimulation electrode (S, Figure 1) was placed in the direct perforant pathway (PP) projection from the entorhinal cortex to field CA1 (Doller & Weight, 1982). The distinctly myelinated PP is adjacent to the hippocampal fissure and comprises, in part, the *stratum moleculares-lacunosum*. CCK-GABA colocalization (Bartfai, 1985; Hendry et al., 1984) and CCK receptors have been reported in this area (Zarbin, Innis, Wamsley, Snyder, & Kuhar, 1983).

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Figure 1. Schematic of a hippocampal slice illustrating a field CA1 pyramidal cell body and dendrites. A recording electrode (R1) placed in *stratum pyramidale* recorded EAPs (illustrated), and a second recording electrode (R2) placed in *stratum moleculare-lacunosum* recorded EPSPs (illustrated). A stimulation electrode (S) placed in the perforant pathway delivered single-pulse or HFS. The vertical calibration for EAPs is 2.5 mV, and horizontal calibration is 5.0 msec. For EPSPs, the vertical calibration is 2.0 mV, and the horizontal calibration is 5.0 msec.

The PP was selected for activation because it is described as a "weak" projection (Colbert & Levy, 1992), and the present experiments required an initial HFS that was subthreshold for induction of neuronal modifications. LTP has been induced in the PP (Doller & Weight, 1982) and LTP and LTD have been reported for other afferents to CA1 pyramidal cells (Stanton & Sejnowski, 1989). HFS consisted of four trains of 10 pulses at 100 Hz, with a 1-sec intertrain interval. Single-pulse stimulation was delivered at 10-sec intervals. Recording electrodes consisted of drawn glass micropipettes filled with 2 N NaCl (5–10 M Ω). Recording electrodes were placed in *stratae pyramidales* (R1) and *moleculare-lacunosum* (R2) to obtain simultaneous recordings of evoked action potentials (EAPs) and excitatory postsynaptic potentials (EPSPs; Figure 1). Pulse duration was varied with a fixed current to obtain the input-output characteristics of the preparation. For control responses, a pulse duration was selected that was *suprathreshold* for EAPs, and for HFS, pulse duration was selected that was *subthreshold* for an EAP. Slope and amplitude measurements were obtained using standard procedures with Neuropro (RC Electronics, Goleta, CA), a PC-based system. Data were normalized to mean control values. Mean differences were evaluated against control values after potentiation or depression using the paired *t* test.

Design and Procedure

Single-pulse-evoked responses were recorded for a 30-min control period with ACSF perfusion. HFS was applied and responses recorded for a 30-min post-HFS period (also with ACSF perfusion). If neither potentiation nor depression of responses was in-

duced, then a 30-min perfusion with one of several concentrations of CCK-8S was initiated. The sulfated octapeptide of CCK²⁶⁻³³ used in these experiments was purchased from BaChem Bioscience, Inc. (Philadelphia, PA). CCK-8S concentrations in the range of 100 nM–2.0 μ M were used in this study.

A second HFS (pulses of the same duration parameter) was applied after 30 min of CCK-8S perfusion, and wash with CCK-8S-free ACSF was immediately initiated. Responses were recorded for a 30-min post-CCK-8S/post-HFS period. A control condition was provided by the application of a second series of subthreshold trains without CCK-8S perfusion.

RESULTS

Figure 2 illustrates the results obtained with 500-nM CCK-8S perfusion in conjunction with HFS. The 500 nM CCK-8S was without significant effect on EAPs (Figure 2A; $p > .05$), but EPSPs were reduced (Figure 2B; $-14.4\% \pm 6.7\%$, $N = 6$, $p < .05$). With concurrent HFS, CCK-8S was associated with a persistent *depression* of both EAPs (Figure 2A; $-45.1\% \pm 14\%$, $N = 6$, $p < .05$) and EPSPs (Figure 2B; $-28.9\% \pm 7.6\%$, $N = 6$, $p < .05$). Depression persisted for at least 30 min in ACSF wash. The reduction in EPSP slope associated with HFS was larger (-28.9% vs. -14.4% , $N = 6$, $p < .05$) than the depression associated with CCK-8S

Figure 2. Effect of 500-nM CCK-8S perfusion with and without HFS on *stratum pyramidales* responses. HFS of the perforant pathway is indicated by four arrows, indicating that four trains (of 10 pulses each) were used (ACSF control and CCK-8S perfusion). EAP (A) and EPSP (B) measurements were normalized to mean control values. Vertical bars indicate standard error of the mean. EAP and EPSP HFS-induced depression differed from control values ($p < .05$, $N = 6$). Inserts illustrate control EAP and EPSP responses (solid lines) and post-CCK-8S/HFS responses (broken lines). Mean baseline EAPs were 2.1 ± 0.10 mV, and mean EPSP slopes were 2.7 ± 0.09 mV/msec.

Figure 3. Effect of 1- μ M CCK-8S perfusion with and without HFS on hippocampal responses. The protocol in Figure 2 was followed. EAP (A) and EPSP (B) HFS potentiation differed from respective control values ($p < .05$, $N = 6$). Mean baseline EAPs were 2.3 ± 0.13 mV, and mean EPSP slopes were 2.3 ± 0.08 mV/msec.

perfusion. Figure 2A shows a slight short-term potentiation of EAPs associated with the initial HFS, which does not appear with concurrent CCK-8S perfusion.

Figure 3 illustrates the results obtained with 1- μ M CCK-8S perfusion using a protocol identical to that described previously. Like 500-nM CCK-8S perfusion, 1 μ M CCK-8S was without effect on EAPs (Figure 3A; $N = 6$, $p > .05$), but EPSPs were reduced (Figure 3B; $-16\% \pm 9\%$, $N = 6$, $p < .05$). With 1- μ M CCK perfusion, HFS was associated with a persistent significant potentiation of both EAPs (Figure 3A; $27\% \pm 13\%$, $N = 6$, $p < .05$) and EPSPs (Figure 3B; $9.4\% \pm 7.0\%$, $N = 6$, $p < .05$). Potentiation persisted for at least 30 min in ACSF wash. Figure 3A also shows a short-term potentiation associated with the initial HFS, which does not appear with concurrent CCK-8S perfusion.

Intermediate concentrations of CCK-8S (not illustrated) were neutral with regard to HFS-associated LTP or LTD. With 750 nM CCK-8S, neither EAPs nor EPSPs was potentiated or depressed following HFS. With 900 nM CCK-8S, only potentiation of the EAP was observed ($17.4\% \pm 5.5\%$, $N = 6$, $p < .05$), whereas EPSPs were unaffected. A CCK-8S concentration $>1.5 \mu$ M was associated with a total depression of EAPs and EPSPs that reversed to baseline levels upon perfusion with drug-free ACSF.

DISCUSSION

These results demonstrate a dose dependence of HFS-induced response modifications with CCK-8S in field CA1 of the hippocampal formation. A relatively low concentration of CCK-8S (500 nM), with concurrent HFS, was associated with a persistent depression of both EAPs and EPSPs, whereas a relatively higher concentration of CCK-8S (1 μ M), with concurrent HFS, was associated with a persistent potentiation of both EAPs and EPSPs. Intermediate concentrations of CCK-8S (750 or 900 nM) were apparently neutral with regard to depression or potentiation, as 750 nM CCK-8S was not associated with response modification, and 900 nM CCK-8S was associated only with potentiation of EAPs.

The mechanism underlying the effect of CCK-8S and the differential induction of potentiation or depression can only be speculated at this time. In several brain areas, a neuropeptide and classical neurotransmitter are located in the same neuron (Bartfai, 1985; Hendry et al., 1984; Hoekfelt et al., 1987). For example, CCK-8S-GABA colocalization is found in the hippocampal formation (Bartfai, 1985; Somogyi et al., 1984), but little is known of their functional relationship. In the case of CCK-8S and dopamine colocalization (Hoekfelt et al., 1980), however, CCK-8S may modulate dopamine release (Voigt, Wang, & Westfall, 1986). CCK-8S modulates GABA release in the rat solitary complex (Branchereau, Champagnat, Roques, & Denavit-Saubie, 1992) and may similarly modulate GABA in the hippocampal formation.

CCK-8S is a potent neuronal excitant in the hippocampal formation (Boehme, Stutzmann, & Blanchard, 1988; Dahl, 1987a, 1987b, 1988; Dodd & Kelly, 1981; Jaffee, Aitken, & Nadler, 1987). In the dentate gyrus, EAP amplitude varies inversely with EPSP amplitude with CCK-8S application (Dahl, 1987a): EAPs increase in amplitude, while EPSPs decrease in amplitude. This finding is consistent with a depolarization from resting potential (Dahl, Bailey, & Winson, 1983; Takeuchi & Takeuchi, 1960), the basis of which may be a CCK-8S-induced reduction of GABA release (Bartfai, 1985; Branchereau et al., 1992), a postsynaptic action of CCK-8S (Buckett & Saint, 1989), or both. The present results indicate that, whatever the locus of CCK-8S modulation, both synaptic activation (EPSP) and neuronal output (EAP) undergo HFS-induced modifications when used concurrently with CCK-8S concentrations. The present results contrast the finding of baclofen/isoproterenol-induced potentiation in the dentate gyrus (Burgard & Sarvey, 1991), in which only the EAP was potentiated while the EPSP was unchanged.

The differential induction of depression or potentiation of neuronal responses may involve the instantaneous membrane potential. In the visual cortex, steady-state membrane potential that is close to, but more positive than, resting potential is associated with HFS-induced LTD, whereas stronger steady-state depolarization is associated with HFS-induced LTP (Artola et al., 1990). In hippocampal field CA1 and the dentate gyrus, steady-state hyperpolarization is associated with HFS-induced LTD, whereas LTP is associated with steady-state depolarizations (Stanton, Chattarji, & Sejnowski, 1991; Xie et al., 1992).

In the dentate gyrus, baclofen (a GABA_B agonist) disinhibits hippocampal neurons via reduction of GABA release (Harrison, 1990; Misgeld, Mueller, & Brunner, 1978). CCK-8S enhanced paired-pulse facilitation in the dentate gyrus in a similar manner (Rich-Bennett, Dahl, & LeCompte, 1992), suggesting a reduction of non-GABA_A-mediated inhibition. In addition, both CCK-8S (Boehme et al., 1988; Buckett & Saint, 1989; Dodd & Kelly, 1981; Jaffee et al., 1987) and baclofen (Burgard & Sarvey, 1991; Misgeld et al., 1978) depolarize hippocampal neurons, further suggesting a CCK-8S-induced reduction of GABA release. In the present study, perfusion with CCK-8S concentrations $>1.5 \mu$ M was associated with a reversible suppression of EPSP and EAP amplitudes. This was attributable to depolarization block (Bunney & Grace, 1978). Similarly, 1 μ M CCK-8S was associated with a reduction of EPSP amplitude, as would likely occur with postsynaptic depolarization (Dahl et al., 1983; Takeuchi & Takeuchi, 1960). This result is also consistent with known depolarizing effects of CCK-8S in field CA1 and the suggestion that CCK-8S induces a reduction of GABA-mediated inhibition. If CCK-8S and GABA are so related, then the results of the present study, demonstrating a dose dependence of potentiation or depression with CCK-8S, are consistent with studies

that link HFS-induced LTP or LTD to membrane potential by injection of hyperpolarizing or depolarizing currents from an intracellular microelectrode (Artola et al., 1990; Xie et al., 1992).

The present results suggest a neuromodulatory function for CCK-8S in hippocampal field CA1, and implicate CCK-8S-containing intrinsic pathways (Handelmann, Meyer, Bienfeld, & Oertel, 1981) in the differential induction of LTP or LTD. The substrates and conditions underlying induction of LTP or LTD are of interest because of their relevance to presumptive biological substrates of memory (Teyler & DiScenna, 1984).

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