β-Adrenergic Mechanisms in Long-Term Potentiation and Norepinephrine-Induced Long-Lasting Potentiation

JOHN M. SARVEY

1. INTRODUCTION

A brief train of high-frequency, repetitive electrical stimulation to the perforant path results in long-term potentiation (LTP) of the response to low-frequency stimulation of that pathway. In the dentate gyrus, LTP is manifested as an increased amplitude of the extracellularly recorded synchronous action potentials (population spike) of granule cells, a decrease in the latency of the population spike, and a steepening of the initial slope of the extracellularly recorded excitatory postsynaptic potential (EPSP) in response to stimulation of the perforant path (Bliss and Lømo, 1973; Bliss and Gardner-Medwin, 1973). Long-term potentiation has also been demonstrated in hippocampal fields CA1 and CA3 (Schwartzkroin and Wester, 1975; Alger and Teyler, 1976). In intracellular recordings, LTP is manifested primarily as an increased EPSP amplitude (Andersen et al., 1977, 1980; Yamamoto and Chujo, 1978; Misgeld et al., 1979; Wigström and Gustafsson, 1985; Barrionuevo et al., 1986).

This phenomenon, which may represent the neural substrate for learning and memory (Swanson et al., 1982; Morris and Baker, 1984; Lynch and Baudry, 1984), has sparked a great deal of interest. Although research efforts have been mounting steadily, its mechanism remains unknown. There is an absolute requirement for extracellular calcium and therefore, apparently, intact synaptic transmission (Dunwiddie et al., 1978; Dunwiddie and Lynch, 1979). A postsynaptic requirement for calcium is suggested by the demonstration that injection of the calcium chelator EGTA into the postsynaptic neuron through an intracellular microelectrode also prevents the development of LTP (Lynch et al., 1983). Phosphorylation of synaptic (Bär et al., 1980; Chapter 46) and nonsynaptic (Browning et al., 1981; Hoch et al., 1984) proteins appears to be correlated with the appearance of LTP and may be involved in its production and/or maintenance. Protein synthesis has
also been implicated in LTP (Duffy et al., 1981; Stanton and Sarvey, 1984). Despite evidence for involvement of calcium, protein phosphorylation, and protein synthesis in LTP, no unifying hypothesis that integrates this information has emerged. It is not even clear whether the mechanism of LTP is presynaptic, postsynaptic, or a combination of both.

Although little is known about neurotransmitter actions in neuronal plasticity, interest has begun to focus on possible involvement of monoamine transmitters in LTP. Depletion of norepinephrine (NE) or serotonin has been shown to inhibit production of LTP in the dentate gyrus of anesthetized rat (Bliss et al., 1983). The inhibition seen by that group could be accounted for purely by decreased potentiation of the EPSP, since the population spike still became enhanced relative to the EPSP after high-frequency trains (HFTs) of repetitive stimulation in NE-depleted animals (Bliss et al., 1983). In contrast, Robinson and Racine (1985), recording from anesthetized or freely moving rats, reported increased potentiation of the EPSP and decreased potentiation of the population spike in reserpine-treated rats. Since both groups recorded both EPSPs and population spikes with a single electrode located in the granule cell body layer or dentate hilus, their contradictory findings might be attributable to inaccuracies in the EPSP measurements. In fact, NE, released during stimulation of the locus coeruleus (Dahl and Winson, 1985) or exogenously applied (Winson and Dahl, 1985), can reduce dendritically recorded EPSPs while not affecting EPSPs recorded at the granule cell soma in anesthetized rats. During repetitive stimulation of locus coeruleus, population spike amplitude increased in 69% of sites tested; but the potentiation did not persist (Dahl and Winson, 1985). In contrast, the population spike was actually depressed during iontophoresis but became potentiated for more than 20 min in 38% of the sites tested (Winson and Dahl, 1985).

Injection of the excitatory amino acid glutamate into the locus coeruleus of anesthetized rats induced a potentiation of the perforant-path-elicited population spike and variable effects on the EPSP recorded in the granule cell body layer. This potentiation, which was sensitive to propranolol, lasted more than 20 min in 37% of the animals tested (Harley and Milway, 1986). Neuman and Harley (1983) also saw no effect of iontophoretically applied NE on the EPSP recorded at the soma in vivo but reported a long-lasting potentiation (LLP) of the population spike in 39% of sites that potentiated in response to NE (30% of all sites exposed to NE). Recording at the granule cell body layer in hippocampal slices, Lacaille and Harley (1985) reported an LLP of both EPSP and population spike following bath application of NE. Similarly, dopamine has been shown to produce an LLP in field CA1 of rat hippocampal slices in vitro (Gribkoff and Ashe, 1984; Ashe, 1984).

In my laboratory, we have sought to investigate the regional specificity of the requirement for NE in LTP as well as the pharmacology and mechanism of action of NE in LTP and LLP. We chose the hippocampal slice preparation because of its stability and amenability to pharmacological manipulations. Slices (400 \( \mu \text{m} \) thick) from adult Sprague-Dawley rats were placed in an “interface” chamber (Schwartzkroin, 1975) at 35°C and perfused from beneath with a modified Krebs-Ringer buffer (Stanton and Sarvey, 1984, 1985a–c). Electrically evoked potentials were recorded in field CA1 and dentate as shown in Fig. 1A. In some experiments, extracellular EPSPs were also recorded by an electrode (not shown) placed in the dendrites where the maximal negative EPSP could be recorded (i.e., corresponding to the level of axons activated by the stimulating electrode). Responses were allowed to stabilize before data were taken. Then, at least three sets of stimulus duration–population spike amplitude curves were taken over a 15- to 30-min period to establish a base line before any drugs were added or a high-frequency train (HFT) of