environment with a variety of patterns for a short period after emergence (*12*). Since there are striking similarities between the phenomena observed in the fly and those observed in vertebrates, it seems that there are also similarities in the neuronal and molecular bases of the modification of the developing nervous system. One possibility is a change in synapses through disuse (*11*).

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5. A small preference for the star target was seen, but was clearly of much smaller magnitude than that shown in Fig. 1, A to E.
6. It may be irrelevant that the dorsoanterior eye regions were not covered by the display, because this region of the eye was not used to test for pattern discrimination.
7. An important problem is the stability or persistence of deprivation effects. Recovery from deprivation effects seems to depend on the length of deprivation and on the conditions of the light environment experienced after deprivation.
8. The rates of arrival in Fig. 2F are lower overall than in those of Fig. 1F, in spite of similar experimental conditions. Reasons for the difference are not evident. But, considering the difference in experimental conditions between both experiments, a possible reason may be a difference in the temperature of the experimental room. The experiments represented in Fig. 1 were performed at 25° to 26°C (in autumn), while those in Fig. 2 were done at 20° to 22°C (in winter). Lowering of temperature may change the flies' general activity. The other possible reason is an effect of diurnal activity rhythms. Experiments represented in Fig. 1 were usually carried out in the evening (4 to 7 p.m.), while those in Fig. 2 were done in the afternoon (1 to 3 p.m.). However, a difference in the rates of arrival (discrimination) is important in the results presented here. The discrimination represented in Fig. 1F was small and was completely different from the tendencies illustrated in Fig. 1, A to E. So, it is reasonable to conclude that discrimination is scarcely possible under these conditions.
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13. Supported in part by a grant-in-aid from the Ministry of Education, Science, and Culture of Japan.

5 June 1985; accepted 2 December 1985

Differential Conditioning of Associative Synaptic Enhancement in Hippocampal Brain Slices

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An electrophysiological stimulation paradigm similar to one that produces Pavlovian conditioning was applied to synaptic inputs to pyramidal neurons of hippocampal brain slices. Persistent synaptic enhancement was induced in one of two weak synaptic inputs by pairing high-frequency electrical stimulation of the weak input with stimulation of a third, stronger input to the same region. Forward (temporally overlapping) but not backward (temporally separate) pairings caused this enhancement. Thus hippocampal synapses in vitro can undergo the conditional and selective type of associative modification that could provide the substrate for some of the mnemonic functions in which the hippocampus is thought to participate.

THE HIPPOCAMPUS IS A CORTICAL structure that has been strongly implicated in certain mnemonic functions (*1*). Some of the information processing that occurs in this region has been described in terms of a general spatiotemporal theory of higher-order Pavlovian conditioning (*2*). Hippocampal synapses can show rapid and persistent (*3*) associative changes when subjected to brief bursts of high-frequency electrical stimulation (*4*). Here we use a pattern of stimulation that shares formal features with differential Pavlovian conditioning to begin to elucidate these changes in the hippocampal brain slice.

Rat hippocampal slices were prepared and maintained in the conventional manner (*4, 5*). Three stimulating electrodes were placed in the Schaffer collateral and commissural projection to region CA1 (Fig. 1A) (*6*). The current delivered to one stimulating electrode [strong (S)] was set to elicit an extracellular synaptic response of approximately 2.5 mV [the strong (S) response]. The current delivered to the other two electrodes [weak 1 (W1) and weak 2 (W2)] was set to give much weaker synaptic responses—between 200 and 300 μV [the weak (W) responses]. Typical W and S synaptic responses are illustrated elsewhere (*4*). All responses were measured with a single extracellular electrode placed in the dendritic region between W1 and W2 (Fig. 1A).

Each weak synaptic input was tested once every 12 seconds, with W2 following W1 by 6 seconds. The continuous testing was punctuated by several types of conditioning trains (Fig. 1B). First, five conditioning trains (100 Hz for 600 msec) were applied to W1 and W2 to verify that such activity alone fails to induce long-term potentiation (LTP) in either of these two W responses (*4*). The interval between the onsets of the stimulation trains delivered to W1 and W2 was 800 msec, and the intertrial interval between each of the five W1-W2 pairings was 6 seconds (Fig. 1B). Second, five conditioning trains (100 Hz for 400 msec) were also delivered to S to verify that such activity alone does not produce heterosynaptic LTP in either of the W synaptic responses (*7*). Third, five conditioning trains were delivered to all three synaptic inputs with either the W1-S or the W2-S forward-pairing scheme (Fig. 1B). During W1-S forward-pairing the W1 trains began 200 msec before the S conditioning trains (forward pairing) and the W2 trains began 600 msec after the S trains (backward pairing); in the W2-S forward-pairing situation, these temporal relationships were reversed (*8*). To assess the effects of W-S pairings, we determined the W1 and W2 amplitudes by calculating the mean of ten consecutive responses obtained during a 2-minute period before and again after W-S pairing. The first 2-minute average was obtained immediately prior to W-S pairing. The second 2-minute average was taken between 12 and 16 minutes after W-S pairing.

Table 1. Synaptic response amplitudes as a function of forward (W+) and backward (W−) pairing. All values expressed as mean ± SEM.

Response	Amplitude		Mean increase (%)
	Before pairing (μV)	After pairing (μV)	
W+	230 ± 18	320 ± 19	42 ± 4
W−	244 ± 17	254 ± 20	5 ± 2

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Differential conditioning trains selectively enhanced the response of the forward-paired pathway. In some experiments, both the W1-S and the W2-S forward-pairing schemes (Fig. 1B) were applied sequentially to the same slice (Fig. 1C) (*9*). Paired W1-W2 conditioning trains and unpaired S trains caused only short-term changes in either W1 or W2 responses (*10*). However the W1-S forward (temporally overlapping) pairing resulted in a persistent enhancement of the W1 synaptic response. By contrast, the W2-S backward (temporally separate) pairing failed to induce associative LTP in the W2 response. To show that W2-S forward pairing was capable of inducing associative LTP in this particular W2 response, we switched to the W2-S forward-pairing scheme. Again, associative LTP only occurred in the forward-paired, W2 response. Thus associative LTP can be induced in either the W1 or W2 synaptic input and is conditional only upon the temporal pairing relationship with S.

Similar results were obtained in 14 slices from ten rats. Seven slices were randomly chosen to receive the W1-S forward pairing and the remaining seven received the W2-S forward pairing (Fig. 1B). For statistical analyses, data were combined from the 14 forward-paired (W+) pathways (W1 results from W1-S forward pairings and W2 results from W2-S forward pairings) and from the remaining 14 backward-paired (W−) pathways. The combined results are summarized in Table 1. Prior to pairing there was (by design) no significant difference (*11*) in the mean amplitudes of the W+ and W− responses ($t(13) = 1.2$, $P > 0.05$). After pairing, the mean W+ response amplitude increased significantly ($t(13) = 19.4$, $P < 0.05$), but there was no significant change in the mean W− response amplitude ($t(13) = 1.5$, $P > 0.05$). Finally, after pairing, the mean W+ response amplitude was significantly larger than the mean W− response amplitude ($t(13) = 3.7$, $P < 0.05$); and, most important, the mean increase in the W+ response amplitude was significantly greater than the mean increase in the W− response amplitude ($t(13) = 12.1$, $P < 0.05$).

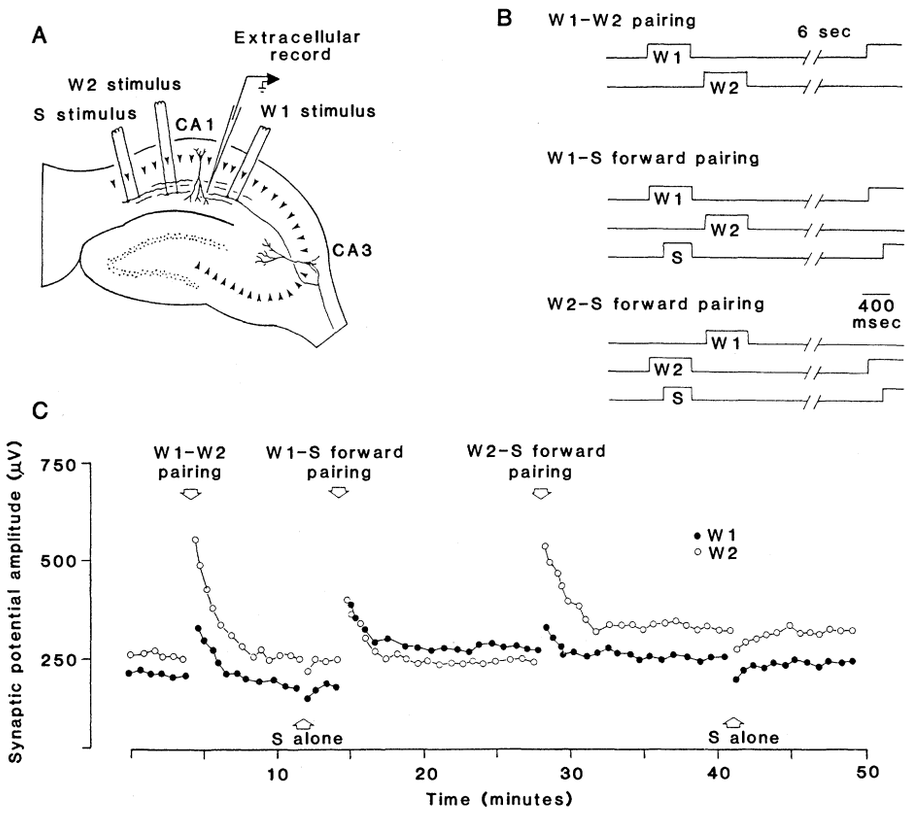

Fig. 1. Differential conditioning of associative synaptic enhancement. (A) Three bipolar stimulating electrodes were placed in stratum radiatum to stimulate Schaffer collateral and commissural fibers projecting to area CA1. The stimulating electrode closest to area CA3 is consistently designated W1. (B) Timing relations for three stimulation patterns. Square pulses indicate the onset and duration of 100-Hz afferent stimulation through the indicated electrodes. The first pattern was used as a control to determine the effects of stimulation of the weak synaptic inputs alone. In the second pattern, W1 was forward-paired with S, while in the third pattern, W2 was forward-paired with S (see text). (C) Results from a slice in which the three stimulation patterns were applied sequentially. W1 (●), W2 (○).

This demonstration of differential and timing-specific induction of associative LTP shows that, in the absence of complex neuronal circuits, hippocampal synapses can express the types of conditional changes that could mediate aspects of associative learning. We have shown that (i) this is an activity-dependent form of neuroplasticity; (ii) the induction of the functional modulation is rapid; (iii) the expression of the enhanced synaptic strength is persistent; (iv) modification of one synaptic input is conditionally dependent upon temporal contiguity or contingency with activity in another synaptic input to the same region (*12*); and (v) the associative enhancement is specific to synapses whose activity conforms to the temporal requirement (*12*). These are also features of the synaptic interactions in certain identified circuits of *Aplysia* that have been demonstrated to mediate behavioral differential Pavlovian conditioning (*13*).

A reasonable working hypothesis is that the mechanism responsible for these plastic properties of hippocampal synapses (*14*) participate in some aspect of the suspected role (*2*) of this cortical circuitry in higher-order Pavlovian conditioning (*15*). The occurrence of this form of synaptic memory in the hippocampal brain slice will enable investigation of associative interactions at the level of synaptic microphysiology and biophysics (*5, 14*). Finally, differential conditioning paradigms can be used to determine the extent to which synaptic modification rules parallel those of higher-order conditioning (*2, 12, 15*).

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9. Generally only one of the two stimulation patterns was applied to each slice. For illustration, Fig. 1C shows both patterns used in succession. We have not applied the two patterns in succession a sufficient number of times to comment on the effect of sequential applications.
10. Stimulation of W alone produces PTP but not LTP (*4*). Unpaired S stimulation either produces a brief heterosynaptic depression or has no effect on the W responses (*4*). The amplitude of the S response was only monitored immediately before each set of trains when stimulation parameters were readjusted to elicit a 2.5-mV S response.
11. All tests were paired *t* tests for dependent means. They were one-tailed because the a priori hypothesis and past experience lead to a unidirectional prediction—a post-pairing enhancement or no change.
12. The temporal contiguity requirements for associative LTP are considered elsewhere [S. Kelso and T. H. Brown, *Soc. Neurosci. Abstr.* **10**, 78 (1984); S. Kelso and T. H. Brown, in preparation]. Explicitly temporal aspects of the role of the hippocampus in conditioning have been proposed to engage and require a variety of neural feedback loops, possibly including some form of efference copy [E. Halgren, in *Neuropsychology of Memory*, L. R. Squire and N. Butters, Eds. (Guilford, New York, 1984), pp. 165–182; R. F. Thompson *et al.*, *ibid.*, pp. 424–442; T. Berger, *ibid.*, pp. 443–461; J. W. Moore and P. R. Solomon, *ibid.*, pp. 462–488].
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16. Supported by NIH grant NS07408, AFOSR contract F49620, and McKnight Foundation Scholar's and Development Awards. We thank G. Clark for valuable comments on an earlier draft of this manuscript.

16 September 1985; accepted 14 January 1986

Vasoconstriction: A New Activity for Platelet-Derived Growth Factor

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Platelet-derived growth factor (PDGF) is a potent mitogen for vascular smooth muscle cells that has been implicated in the pathogenesis of atherosclerosis. The potential role of PDGF in the altered vasoreactivity of atherosclerotic vessels has been studied through an examination of its effects on contractility in the rat aorta. PDGF caused a concentration-dependent contraction of aortic strips and was significantly more potent on a molar basis than the classic vasoconstrictor peptide angiotensin II. Furthermore, PDGF increased the cytosolic free calcium concentration in cultured rat aortic smooth muscle cells. These observations suggest a new biological activity for PDGF that may contribute to the enhanced vasoreactivity of certain atherosclerotic vessels.

PLATELET-DERIVED GROWTH FACTOR (PDGF), a cationic protein of platelet alpha granules, is a potent mitogen in vitro for vascular smooth muscle cells (VSMC) (*1*). In addition, PDGF in vitro causes migration of VSMC as well as of fibroblasts and inflammatory cells (*2*). On the basis of these activities it has been proposed that PDGF, released at sites of vascular injury, plays a significant role in the development of atherosclerosis, particularly in VSMC migration into and proliferation in the intima (*3*). Although contraction and maintenance of tone are the major physiologic functions of VSMC, the consequences of mitogenic stimulation, as occurs in atherosclerosis, on these physiologic functions of VSMC have not been considered. Because both experimental and clinical coronary artery spasm occur predominantly at the site of atherosclerotic lesions (*4*) and because atherosclerotic lesions are thought to have increased basal tone (*5*), it has been suggested that some features of this disease are responsible for the hypercontractility seen basally and in response to agonists such as ergonovine, histamine, and serotonin (*6*). We have proposed that mitogenic influences acting on VSMC in atherosclerotic arteries may contribute to the enhanced contractile responsiveness (*7*). This seems plausible because (i) certain mitogens (including PDGF) mobilize intracellular calcium in several cell types (*8*), and (ii) agonist-mediated increases in cytoplasmic calcium result in a contractile response in VSMC (*9*). PDGF is the mitogen generally considered to be the most important in stimulating the proliferation of VSMC in atherosclerosis (*3*). To test the hypothesis that PDGF can mediate contraction in VSMC, we assessed its contractile effects on rat aorta and its ability to mobilize calcium in cultured rat VSMC. To evaluate the relative potency of PDGF as an agonist, we compared its vasoactive effects with those of the potent vasoconstrictor angiotensin II.

The effects of purified human PDGF on contractile tension in isolated rat aortic strips are illustrated in Fig. 1. The PDGF used in these experiments was purified to more than 99 percent homogeneity accord-

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