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RAPID COMMUNICATION

Inhibition of Long-Term Potentiation by an Antagonist of Platelet-Activating Factor Receptors

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Platelet-activating factor (PAF) is a potent membrane-derived agent that triggers shape change, secretion, and aggregation in blood platelets. It also causes increases in intracellular calcium levels and a variety of functional effects in cells other than platelets. Recent work indicates that PAF accumulates in brain during ischemia and convulsions (Kumar, Harvey, Kester, Hanahan, & Olson, 1988), that PAF receptors are found in synaptic membrane fractions, and that antagonists of the PAF receptor protect neurons from the pathophysiological effects of ischemia (see Marcheselli, Rossowska, Domingo, Braquet, & Bazan, 1990). The functions of PAF in brain are unknown but, in light of its effects on blood platelets, it is conceivable that the factor promotes structural changes in synapses. In support of this idea are reports that inhibitors of phospholipase A_2, the enzyme that catalyzes the initial steps of PAF synthesis, interfere with the induction of long-term potentiation (LTP) (Linden, Sheu, Murakami, & Routtenberg, 1987; Okada, Yamagishi, & Sugiyama, 1989), a type of physiological plasticity associated with modifications of synaptic morphology. Here we describe experiments showing that a competitive antagonist of the PAF receptor blocks the formation of LTP.

Hippocampal slices were prepared and maintained in an interface chamber using conventional techniques. An extracellular recording pipette was positioned in the apical dendritic zone (stratum radiatium) of field CA1b and two stimulating electrodes were placed into fields CA1a and CA1c so as to activate separate populations of Schaffer-commissural axons. Responses were collected to single pulses delivered one/20s for

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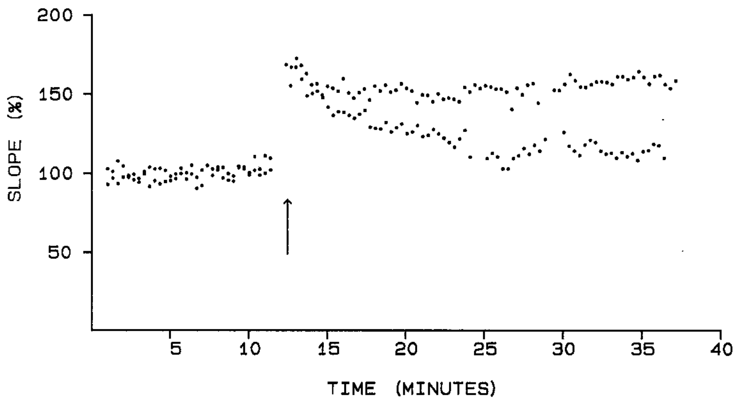

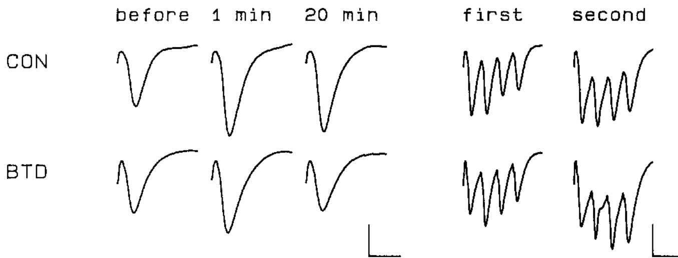

FIG. 1. Changes in the slopes of synaptic responses elicited by theta burst stimulation (arrow) in a slice prior to and 40 min after administration of a PAF receptor antagonist. (Top) Slopes of field EPSPs elicited by single stimulation pulses delivered once/20s expressed as a percentage of the mean value of responses obtained prior to theta burst stimulation. The pathway that exhibited LTP was stimulated prior to drug administration while the input which did not show stable potentiation was given theta bursting after drug application. (Bottom) Individual field EPSPs and theta burst responses for the two pathways are shown. Calibration bars: 1 mV/10 ms for the field potentials and 2 mV/20 ms for the burst responses.

10–30 min following which attempts were made to elicit LTP using theta burst stimulation either in the presence or absence of 2,5-bis(3,4,5-trimethoxyphenyl)-1,3-dioxolane (BTD), a compound which is closely related to the diaryltetrahydrofuran class of PAF receptor antagonists. The drug, which has a K_i of 0.3 μM in a washed platelet assay (Corey, Chen, & Parry, 1988), was infused for 35–50 min prior to high-frequency stimulation at a final concentration of 8 μM (12 experiments) or 24 μM (2 experiments).

Infusion of BTD had no obvious effects on the size or shape of field EPSPs; the mean percentage change in the initial slope of the negative going field potential was -2% (n = 14) at 30 and 40 min after the onset

TABLE 1
Effects of a Platelet-Activating Factor Antagonist on the Magnitude of LTP Induced by Theta Burst Stimulation

	Percentage change from baseline vs. minutes after theta burst stimulation ($\overline{X}$ ± SD)					
	5 min	10 min	15 min	20 min	25 min	30 min
Control ($n = 18$)	63 ± 24%	50 ± 19%	47 ± 18%	44 ± 18%	43 ± 19%	42 ± 21%
Experimental ($n = 14$)	28 ± 13%	20 ± 12%	14 ± 10%	11 ± 13%	5 ± 14%	5 ± 12%
	Percentage of group showing various amounts of potentiation at 30 min after theta burst stimulation					
	0–9%	10–19%	20–29%	30–39%	40–49%	>50%
Control ($n = 18$)	6%	11%	6%	22%	22%	33%
Experimental ($n = 14$)	71%	14%	7%	7%	0%	0%

of drug administration. Figure 1 illustrates an experiment in which attempts were made to induce LTP from one collection of inputs to CA1 prior to BTD application and in a second set 40 min following infusion of the compound. As is evident, robust LTP was obtained in the first case but not in the second. BTD in this experiment did not prevent the immediate increase in synaptic responses elicited by theta burst stimulation (an effect previously shown to be dependent upon NMDA receptors) but largely blocked the development of stable potentiation. Table 1 summarizes the data for the control and drug-treated groups. A reduction in the degree of potentiation was evident by 5 min after high-frequency stimulation in the BTD group (top), and by 25 min later only a small number of the slices exhibited an LTP effect (bottom). The differences between the groups were statistically significant ($p < .001$, Mann–Whitney U test) at each time point tested.

The suppressive effects of the receptor antagonist on potentiation could be mediated via an action on the synaptic responses elicited during high-frequency bursts (i.e., on the initial trigger for LTP) or on the cellular events that immediately follow the bursts (i.e., on LTP development). The theta burst stimulation paradigm has the advantage of producing a stereotyped pattern of postsynaptic responses (including a defined NMDA receptor-mediated component) and thus allowing for tests of drug-elicited effects on the initial triggering events for LTP (see Fig. 1, lower right). Accordingly, we compared the area of the field potentials obtained during theta burst stimulation in the presence ($n = 8$) vs absence ($n = 8$) of the receptor antagonist. The mean areas (arbitrary units) of

the first, second, fifth, and tenth burst responses for the control group were 70 ± 16, 133 ± 38, 126 ± 34, and 108 ± 32 ($\bar{X}$ ± SD), while the equivalent values for the drug-treated slices were 78 ± 15, 149 ± 31, 131 ± 27, and 118 ± 27. From this we conclude that BTD had little if any effect on the theta bursting responses that normally generate LTP. Further analysis of the control slices revealed that the extent to which the area of the responses decreased over the course of ten stimulation bursts was negatively correlated with the degree of LTP induced. Thus, the ratio of the area of the tenth burst response to the area of the second burst response was correlated with the percentage LTP present at 10 min after high-frequency stimulation (r = .83). This predictive parameter was not detectably different in the control and experimental slices (83 ± 13% in controls and 80 ± 9% in experimentals; $\bar{X}$ ± SD). This result strongly suggests that BTD acts on the development of LTP rather than on its initial induction stages.

As noted above, PAF accumulates in brain during ischemia and seizures, and it is thus not unreasonable to hypothesize that local increases in the factor occur in the period immediately after intense synaptic activity. This could be mediated by calcium influx via NMDA receptors and subsequent activation of phospholipase A_2. The mechanisms by which PAF receptors might promote LTP are subjects for future research, but it is noteworthy that PAF elicits growth responses in cultured neurons (Kornecki & Ehrlich, 1988) and shape changes followed by aggregation in platelets. LTP is accompanied by structural changes in spines and possibly by the formation of synaptic contacts, and it is not unlikely that PAF contributes to these effects. In general, the present findings add another component to the list of platelet transformation events that occur as part of LTP and thus support the idea (cf. Staubli, Vanderklish, & Lynch, 1990) that the potentiation effect is a special case of the general phenomenon of shape change and adhesion.

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