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BRAIN RESEARCH

Research Report

Platelet-activating factor contributes to the induction of long-term potentiation in the rat somatosensory cortex in vitro

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ABSTRACT

The contribution of platelet-activating factor (PAF) to the induction of neocortical LTP was examined in rat brain slices containing the primary somatosensory cortex (SI). Field potentials evoked by single pulse stimulation in cortical layer IV were recorded from layer II/III. In control experiments, tetanic high frequency stimulation (HFS) resulted in input-specific, NMDA receptor-dependent LTP (21.1±3.2%; mean±SEM; n=15; P<0.001). BN-52021 (5 μM), an antagonist at the extracellular PAF receptor, weakened the HFS-induced LTP to 12.4±2.7% (n=11; P<0.05). In contrast, HFS-induced LTP was significantly enhanced to 29.4±2.3% (n=11; P<0.05) when brain slices were superfused with ACSF containing the PAF receptor-agonist C-PAF (1.5 μM). The difference between LTP weakened by BN-52021 and LTP enhanced by C-PAF was highly significant (P<0.0005). These results suggest a physiological contribution of PAF to the induction of LTP in neocortical area SI. This contribution of PAF is mediated by an action at extracellular receptor sites.

1. Introduction

Platelet-activating factor (PAF) is a lipid-soluble messenger molecule derived from membrane phospholipids with various physiological functions in the organism, including the CNS (Bussolino et al., 1995; Ishii and Shimizu, 2000; MacLennan et al., 1996; Bazan, 2005). Extra- and intracellular receptors of PAF have been identified (Marcheselli et al., 1990). In addition to the contribution of PAF to physiological functions, the involvement of this messenger in pathophysiological alterations of brain function has been reported (for review see MacLennan et al., 1996). Concerning normal brain functions, recent experiments suggest an involvement of PAF in long-term potentiation (LTP) of synaptic transmission, i.e., an activity-dependent enhancement of synaptic strength. LTP is thought to be important for the adaptation of behavioral functions, as well as in higher functions such as learning and memory (for review see e.g. Bear, 1998; Roman et al., 1999). In the hippocampus, competitive antagonists at the extracellular PAF receptor have been shown to inhibit the induction of LTP in the CA1 region (Arai and Lynch, 1992; Del Cerro et al., 1990; Kato et al., 1994; Kondratskaya et al., 2004) as well as in the dentate gyrus (Kato and Zorumski, 1996). Supporting evidence comes from results on synaptic plasticity in transgenic mice bearing a deficiency in the PAF receptor (Chen et al., 2001). In these animals hippocampal LTP was attenuated. Furthermore, PAF was demonstrated to contribute to the induction of LTP in brainstem vestibular nuclei (Grassi et al., 1998). Concerning basic synaptic functions, it was demonstrated that the application of either PAF or a PAF analogue resulted in an increase of synaptic transmission in the hippocampus (Clark et al., 1992; Kato and Zorumski, 1996; Kornecki et al., 1996; Wieraszko et al., 1993) as well as in vestibular nuclei (Francescangeli et al., 1997; Grassi et al., 1998). Presumably,

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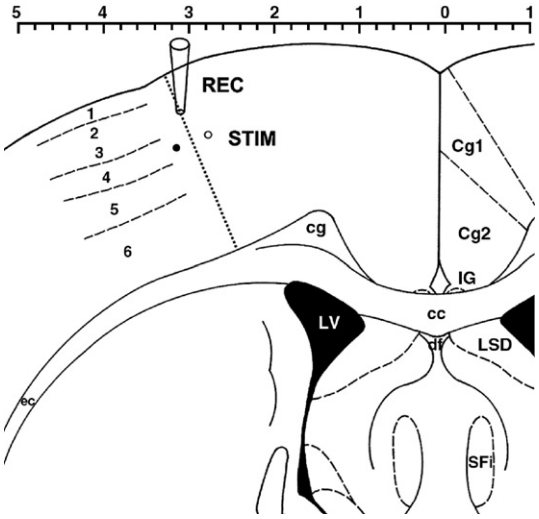

Fig. 1 – Arrangement of recording (REC) and stimulation (STIM) sites in cortical brain slices. Recording site in layer II/III is indicated by the symbol of a glass microelectrode, while the two stimulation sites in layer IV are indicated by a filled circle (HFS site) and an open circle (control site), respectively. The dotted line represents a vertical cortical reference column including the recording site. The margins between cortical layers are roughly indicated by dashed lines. Cg, cingulate gyrus; cc, corpus callosum; cg, cingulum; df, dorsal fornix; ec, external capsule; LV, lateral ventricle; IG, indusium griseum; LSD, lateral septal nucleus; Sfi, septofimbrial nucleus. The scale on top is in millimeter relative to the medial fissure. Adopted from Paxinos and Watson (1986; plate 19).

these effects of PAF are due to an action on presynaptic receptor sites (Clark et al., 1992; Kato and Zorumski, 1996; Grassi et al., 1999). Based on these results, PAF has been considered a likely candidate for a retrograde messenger in the induction of LTP (Goda, 1994; Kato et al., 1994; Kornecki et al., 1996). However, negative or contradictory results have been reported as well (e.g., Kobayashi et al., 1999). Thus, the participation of PAF in the induction of LTP remains a matter of debate.

In the neocortex, LTP can be induced in a similar way as in the hippocampus (Bear and Kirkwood, 1993; Kirkwood et al., 1993). The functional importance of neocortical LTP is discussed mainly in the context of reorganization of cortical maps in sensory and motor areas (Buonomano and Merzenich, 1998; Dinse and Boehmer, 2002). Furthermore, neocortical LTP is suggested to be of physiological relevance for learning and memory (Bear, 1998; Rioult-Pedotti et al., 1998, 2000) as well as for the recovery of cortical tissue from injury (Hagemann et al., 1998; Nudo, 1999).

In cortical tissues, the presence of PAF receptors (Marcheselli et al., 1990) as well as of PAF itself has been demonstrated (Baker and Chang, 1993; Tiberghien et al., 1991), suggesting a potential involvement of PAF in the induction of LTP in the neocortex. Thus, the present study was performed to examine the physiological contribution of PAF to the induction of LTP in the adult rat primary somatosensory cortex (SI). The induction of LTP in SI during simultaneous blockade or activation of PAF receptors revealed a modulating role of PAF in the induction of neocortical LTP.

2. Results

Field potentials (FP) were evoked by repetitive single pulse stimulation in cortical layer IV and were recorded from layer II/III (Fig. 1). High-frequency stimulation (HFS) was applied using one of the latter stimulation electrodes. In a series of control experiments, HFS induced an increase on the amplitude of the FP component *s1* evoked from the HFS site (Fig. 2A). This HFS-induced potentiation was blocked by simultaneous application of the NMDA receptor-antagonist APV (Fig. 2B). HFS-induced potentiation of *s1* outlasted the observation period of at least 75 min after termination of HFS (Fig. 3, open squares). By contrast, the amplitude of the FP component *s1* evoked from the control stimulation site was only weakly affected by HFS (Fig. 3, filled squares). During the period from 30 min to 40 min after termination of HFS, the mean increase of *s1* evoked from the HFS site and the control stimulation site was 21.1±3.2% ($n=15$, $P<0.001$) and 4.8±1.9% (n.s.), respectively. Based on these results, the long-lasting effect of HFS on FP component *s1* evoked from the HFS site was interpreted in terms of an input-specific LTP.

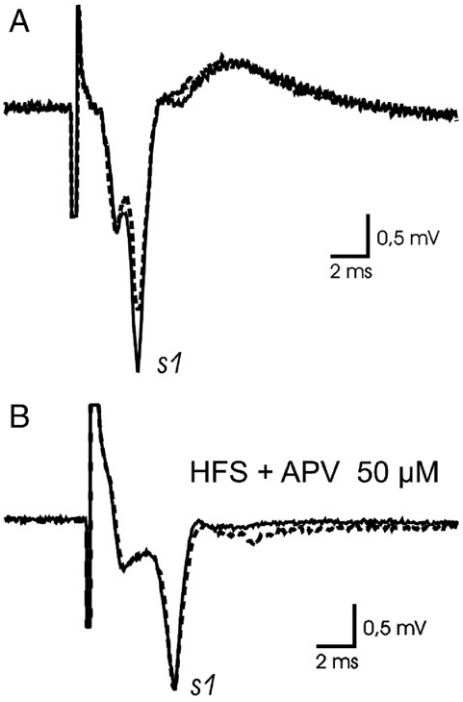

Fig. 2 – HFS-induced LTP of the FP component *s1* and its dependence on NMDA receptor activation. (A) Component *s1* of FP evoked in layer II/III by stimulation in layer IV of SI 30 min after termination of HFS (continuous line) is compared with *s1* during the control period (dashed line). (B) HFS-induced potentiation of *s1* is blocked by the NMDA receptor antagonist APV. In both panels, stimulus artifact is digitally cut.