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Potentiation of prelimbic field potentials during and seconds after trains of excitations in the rat hippocampo-prefrontal pathway

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Abstract

Field potentials were recorded in the prelimbic cortex of anaesthetized rats after excitations of the hippocampo-prefrontal pathway. Stimuli were delivered to the hippocampal CA1 region and short-term changes of field potential amplitudes were observed in two situations. (1) Amplitudes were monitored during trains of stimulations given at frequencies between 1 and 20 Hz. Within trains, potentiation was followed by depression. Both types of changes were frequency dependent. (2) The time course of recovery from within-train plasticity was obtained from field potentials evoked at varying intervals after trains. This revealed a post-train potentiation having a maximum after 2–4 s and lasting for approximately 10 s. The maximal post-train potentiation was nearly independent of the frequency of the preceding train.

Keywords: Rat; Hippocampus; Prefrontal cortex; Prelimbic area; Field potentials; Synaptic potentiation; Synaptic depression

Studies of single unit activity in the rat prelimbic cortex have revealed the presence of neurons engaged in long-term associative learning [15]. This mnemonic involvement has been corroborated by observations of a blocking effect on spatial long-term acquisition induced by prelimbic injections of an antagonist selective to metabotropic glutamate receptor subtype 1 [16]. In accordance with a long-term memory function of the prelimbic cortices, long-term potentiation (LTP) of prelimbic synapses has been observed both in prefrontal slices [17] and in anaesthetized specimens [7]. LTP has also been recorded in freely moving specimens in relation to acquisition in a learning task [4].

In addition to involvement in long-term memory, the prelimbic cortices are also engaged in short lasting working memory [12]. This has been indicated from the effects of neurotoxic lesions [3] and has been supported by observations of neurons displaying sustained post-sensory excitation during maintenance of working memory [1,11]. In spite of this working memory function, little is known about prelimbic synaptic plasticity within the short life-span of working memory – as well as during the period of preceding sensory excitation encoded into working memory. A comprehensive study of prelimbic plasticity during trains of excitations has only been carried out in prefrontal slices [6]. Some knowledge about prelimbic short-term plasticity in vivo comes from so-called paired pulse experiments using the hippocampo-prefrontal pathway [13,14]. Since the paired pulse experimental procedure is not designed to investigate changes of synaptic efficiency during the course of trains of excitations, it became the first objective for the present work to observe the time course of changes in amplitudes of evoked field potentials (EFPs) within trains evoked in the hippocampo-prelimbic pathway. The cited paired pulse results revealed paired pulse facilitation indicating that progressive facilitation might appear during trains. This implication was presently tested for trains covering a range from 1 to 20 Hz.

Secondly, in order to investigate the possible presence of prelimbic synaptic changes having a short life-span, field potential amplitudes were also analyzed during the seconds that followed trains of excitations. Although several reports have described LTP persisting for minutes and hours after trains, no analysis of amplitudes during the first post-train seconds has been found.

Adult PVG rats were anaesthetized with avertin (tribromo-ethanol) (200 mg/kg i.p.) and placed in a stereotaxic instrument (David Kopf, USA). After the initial injection,

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avertin was applied continuously during experiments at a rate of 0.6 ml/h per 100 g and a concentration of 20 mg/ml. Rectal temperature was kept at 36 °C using a homeothermic heating pad. Experiments were performed with permission from the Animal Experiments Inspectorate under the Danish Government Justice Department.

Recording electrodes were made from insulated Pt/Ir wire (diameter: 75 μm) and were positioned 3.7 mm anterior to bregma at a depth of 3.2 mm below the surface, 0.8 mm lateral to the midsaggital suture in the right hemisphere. Stimulation electrodes made from two twined wires were placed dorsally in the hippocampus of the right side of the brain at coordinates 6.3 mm posterior to bregma, 5.3 mm lateral and 3–3.4 mm below the dorsal surface. EFP amplitudes were investigated in ten animals using these coordinates. Additionally, in order to compare the shape of EFPs with those reported earlier in the hippocampo-prelimbic pathway [7], the stimulating electrodes were in five experiments placed at the same ventral hippocampal coordinates used in previous studies: 6.5 mm posterior to bregma, 5.6 mm lateral and 5.2–5.6 mm below the dorsal cortical surface. Positions of recording and stimulating electrodes were visualized in slices stained with cresyl violet.

Stimulation patterns were generated by sequencer programs controlling the output of a '1401-plus' D/A-converter (CED, UK) connected to a stimulator (A365, WPI, UK). EFPs were amplified (gain 1000), filtered (bandpass 0.1 Hz to 3 kHz) and sampled by the 1401-plus A/D-converter. Stimuli of 0.4 ms duration were delivered at a current intensity that gave half-maximal EFP amplitudes: 158 ± 25 μA (mean ± SEM, $n = 10$). At the beginning of experiments stimuli were given every 20 s until EFP amplitudes had reached a steady level. Subsequent trains consisted of 20 stimuli (frequencies are stated below). Prior to each train, ten EFPs were induced at 10 s intervals and their average amplitude served as a reference (A_{ref}) for amplitudes recorded during the ensuing train. After a train, the time course of recovery to pre-train amplitude was investigated in the following way: in each experiment, nine trains were evoked at intervals of a minimum of 2 min. Following each, a single EFP was elicited after one out of nine different delays (see Fig. 3A). The sequence of delays was randomized among the nine values. Post-train amplitudes were expressed as a percentage change from pre-train A_{ref}. Paired pulse plasticity was also observed using stimulus intervals of 50, 77, 100, 133, 200, 333 and 1000 ms (Fig. 1). The amplitude of the second EFP was expressed as a percentage change from the first. Off-line data analysis was made with SPIKE2 supplemented by SCRIPT programs calculating amplitudes of EFPs. The amplitude of the negative peak (Fig. 1, inset) was measured as the difference between the minimum potential level and the preceding potential level at zero slope ($dV/dt = 0$). Presented mean values and standard errors of means were obtained from the

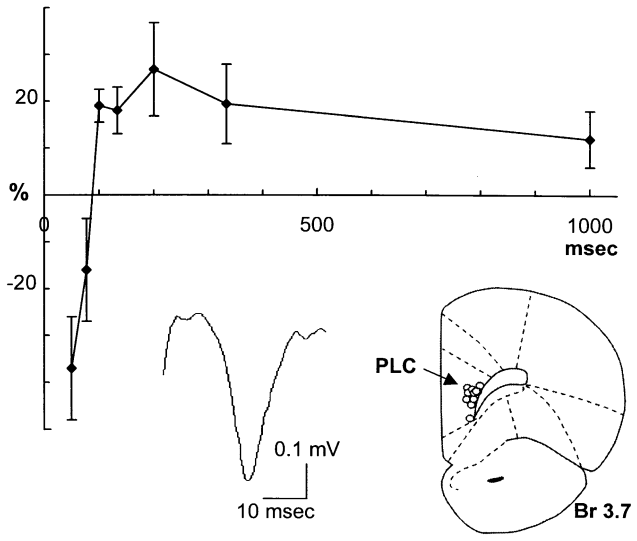

Fig. 1. Paired pulse plasticity of field potentials. The percentage change of a second field potential compared to the first of a pair is shown as a function of the inter-stimulus interval (means ± SEM). Left inset: a field potential evoked by stimulation of the dorsal hippocampal CA1 region. Right inset: coronal section of the right prefrontal cortex 3.7 mm anterior to bregma (Br). Positions of the tips of recording electrodes are shown within the prelimbic cortex (PLC).

group of ten rats stimulated at dorsal hippocampal coordinates.

As a result of dorsal hippocampal stimulation, a prelimbic EFP arose with an average peak delay of 22 ± 0.5 ms (Fig. 1, inset). In order to compare these potentials to earlier reported ones evoked in the ventral CA1/subicular region [7,13], this area was stimulated in five experiments. The resulting EFPs had a shape that closely resembled the one in Fig. 1, but appeared with a slightly shorter peak delay (18 ms).

Paired pulse stimulation (Fig. 1) showed depression at the lowest inter-stimulus intervals, while at higher intervals paired pulse facilitation was present. The course of EFP amplitudes during trains of more than two stimuli is seen in Fig. 2. Trains evoked at frequencies of 1–10 Hz started out with potentiation. However, at frequencies above 3 Hz, potentiation was transient and became replaced by depression. As the frequency rose, depression occurred earlier and with increasingly negative slopes. At the highest frequency tested (20 Hz) depression set in immediately.

Following trains of 10 Hz, the time course of recovery to pre-train amplitudes was observed in eight experiments and mean post-train amplitudes are shown in Fig. 3A. From the depressed amplitude of the last average EFP in trains of 10 Hz (Figs. 2B and 3A at time = 0) the EFP became potentiated 1 s later and reached maximal potentiation after 2–4 s. Subsequently, amplitudes subsided to pre-train size in the course of approximately 10 s. In each experiment, a recovery curve was compiled from nine trains followed by a single test EFP placed after a varying interval. The use of only one rather than more post-train EFPs prevented any

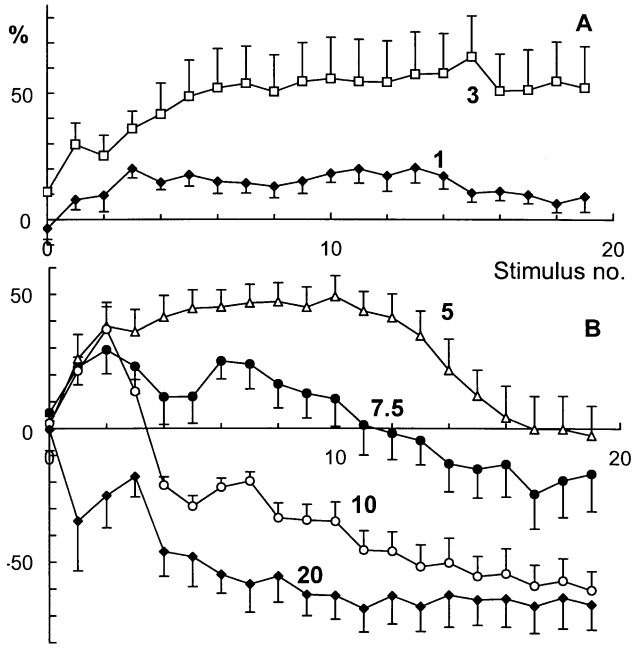

Fig. 2. Time course of field potentials during short trains evoked at various frequencies (stated in Hz at the curves). Amplitudes are shown as a percentage change from an average amplitude of ten pre-train field potentials (means ± SEM, $n = 10$).

plasticity induced by a first post-train EFP from influencing later post-train EFPs. The resulting requirement for nine repeated trains in each experiment could conceivably have caused a change of amplitudes between trains, thereby distorting the recovery curve. In order to test this possibility, a two-way ANOVA (stimulus no.-by-train no.) was made for the eight experiments. The comparison gave no significant effect of train no. ($P > 0.05$) and therefore showed an absence of depression or potentiation persisting for minutes.

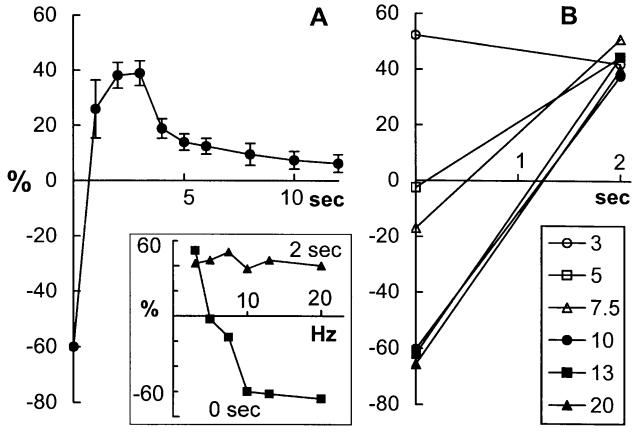

Fig. 3. (A) Time course of post-tetanic potentiation following a train of 20 field potentials evoked at 10 Hz. The points show mean amplitudes ± SEM obtained at varying times after 10 Hz trains. (B) Post-tetanic potentiation recorded 2 s after trains of various frequencies. The trains ended at frequency dependent amplitudes (see Fig. 2) and the magnitude of the last field potential is shown at time = 0 s. Train frequencies are stated in Hz at the bottom. (A, inset) Two curves are shown as a function of the frequency of the preceding train. One (marked '0 sec') shows the amplitudes at which trains ended while the other (marked '2 sec') shows amplitudes 2 s later. Mean values from eight experiments are presented as a percentage change from pre-train amplitudes.

Frequency dependency of post-train potentiation was analyzed by measuring amplitudes of test EFPs placed 2 s after trains of various frequencies (Fig. 3B). The average amplitudes at the completion of trains (Fig. 2) are shown in Fig. 3B (at time = 0) and are compared to the average amplitudes 2 s later. The level of potentiation at this time was nearly independent of the frequency of the inducing train (the relationship is show in the inset of Fig. 3A, marked '2 sec'). This independence was contrasted by highly frequency controlled amplitudes at the end of trains (inset of Fig. 3A, marked '0 sec').

The hippocampo-prefrontal pathway emanates from the CA1/subicular region and projects to the prelimbic cortex [5,8,10] where it excites EFPs mediated by AMPA receptors [9]. These EFPs displayed paired pulse facilitation (Fig. 1) as reported earlier [13,14] but also showed paired pulse depression at the shortest inter-stimulus intervals. Accordingly, trains of the highest frequency in Fig. 2 (20 Hz) began directly with synaptic depression. The facilitation seen in paired pulse experiments at lower frequencies (Fig. 1) continued further within trains (Fig. 2) but was soon influenced by an opposite depressive process increasing with train frequency. In the case of 1 Hz stimulation where no depression was seen during trains of 20 stimuli (Fig. 2), a prolongation to 100 stimuli revealed depression later into trains (unpublished data). Such depression during long trains of 1 Hz stimulation has been reported earlier [2]. In the present experiments, train frequencies of 5, 10 and 20 Hz were used, doubled at each increment. But frequencies were not doubled again to 40 Hz (or beyond) since the EFP peak delay of 22 ms meant that inter-stimulus intervals of 25 ms (or below) would place stimulus artefacts on top of the previously evoked potential and distort measurements of amplitudes.

After excitation of trains that brought EFPs to depressed levels, amplitude recovery displayed an 'overshoot' of post-train potentiation above the pre-train level. Taken together, the present results on EFP changes in the time domain of seconds – along with previous studies of LTP analyzed for minutes and hours [12] – show that the prelimbic synapses can display three sequential types of potentiation. First, an early but transient within-train potentiation appears (Fig. 2). Next, a post-activity potentiation is present for about 10 s (Fig. 3A), and finally after trains of higher frequencies, LTP sets in. Although a correlation between prelimbic LTP and memory consolidation has already been described [12], no analogous relationship between the present type of short lasting post-train potentiation and post-sensory working memory (also lasting for seconds) has been reported. Such memory is related to post-sensory sustained excitation in the prelimbic area [11] and previous observations of post-train potentiation in prelimbic slices have led to the suggestion

that potentiation could contribute to the excitation [6]. The possible existence of such a causality in awake specimens was not contradicted by the present demonstration that short lasting prelimbic post-train potentiation is present during anaesthetized whole animal recordings. Furthermore, there was an approximate coincidence between the life-span of post-train potentiation and the duration of sustained post-sensory excitation in working memory related neurons as studied in delay tasks.

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