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Long term potentiation in the magnocellular medial geniculate nucleus of the anesthetized cat

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Long term potentiation (LTP) has been suggested as a mechanism in learning. The magnocellular division of the medial geniculate nucleus (MGm) is known to develop discharge plasticity rapidly during behavioral learning. The ability of the MGm also to develop long term potentiation was studied in cats under barbiturate anesthesia. Monosynaptic responses elicited in the MGm by periodic (0.2 Hz) stimulation of the brachium of the inferior colliculus (BIC) developed significant increases in amplitude and decreases in latency, which were maintained for at least 1 h, following brief high frequency stimulation of the BIC. Antidromic responses recorded in the inferior colliculus were unchanged. These findings provide a link between learning-induced physiological plasticity and LTP, and demonstrate that the auditory system can develop long term potentiation.

The persistent facilitation of synaptic transmission following brief high frequency electrical stimulation has been investigated extensively in the hippocampus, and is generally referred to as either long lasting or long term potentiation (LTP)[16]. LTP, which is most often characterized by increased amplitudes and decreased latencies of evoked responses, has been observed to last from hours in the anesthetized preparation[3] to days and even months in the unanesthetized preparation[2,6]. Because of the time course and ease of initiation of LTP, and since the hippocampus may be involved in memory storage[5,14], it is possible that LTP is closely related to the physiological processes underlying learning and memory.

Electrophysiological studies of learning have demonstrated that regions of the auditory system undergo systematic physiological change during learning[4,17]. One such region is the magnocellular division of the medial geniculate nucleus (MGm), which receives multisensory inputs and projects to all subdivisions of the auditory cortex[9]. The MGm is highly plastic and exhibits a systematic increase in neuronal evoked activity to an acoustic conditioned stimulus during the acquisition of a behavioral conditioned response[1,15,17]. Because of the postulated link between LTP and learning, we investigated the possibility that the MGm could develop an LTP-like phenomenon following the repetitive activation of its major input, the brachium of the inferior colliculus (BIC)[11,12]. A preliminary report of these findings has been presented[8].

The experiments were performed on anesthetized (40 mg/kg pentobarbital sodium i.p.) adult mongrel cats. Following preparatory surgery, a bipolar stimulating electrode and a monopolar recording electrode were placed stereotaxically into the BIC and MGm, respectively. In some experiments, a second recording electrode was placed in the inferior colliculus to investigate the antidromic BIC volley (Fig. 1A). Stimulation was provided by a constant current stimulator (Grass S88): current levels were 0.1 0.8 mA. To begin testing, stimuli (0.1 ms, 0.2 Hz) were pre-

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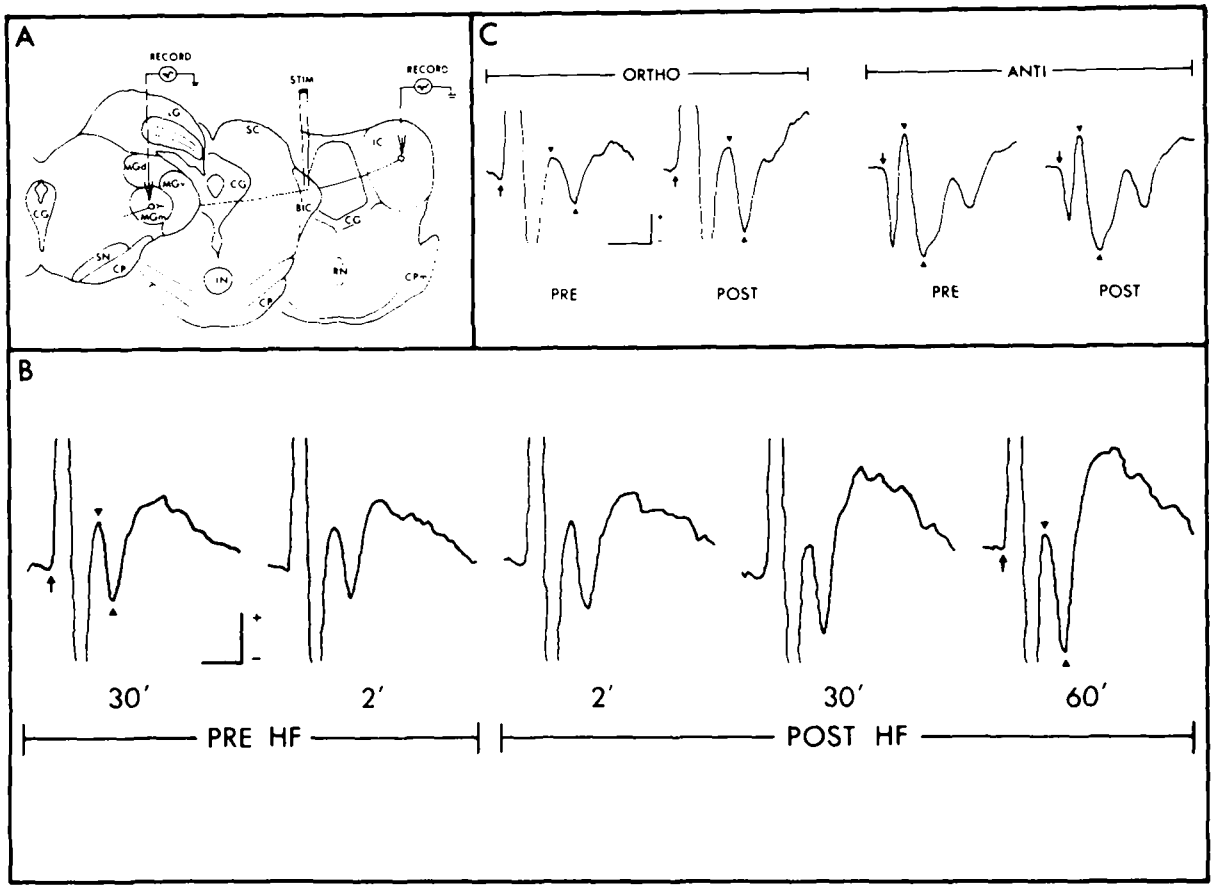

Fig. 1. A: schematic representation of electrode placements in medial geniculate magnocellularis (MGm), brachium of the inferior colliculus (BIC) and inferior colliculus (IC). B: representative MGm responses to BIC stimulation at various times before (PRE) and after (POST) high frequency (HF) stimulation of the BIC. C: representative MGm (ORTHOdromic) and IC (ANTIdromic) responses to BIC stimulation 5 min before (PRE) and 40 min after (POST) HF stimulation of the BIC. Horizontal bars are 1 ms; vertical bars are 100 μV. Arrows indicate time of stimulus; triangles indicate points used for amplitude and latency measurements.

sented to the BIC at various intensities (10–80 V) to generate stimulus–response curves. An intensity, suprathreshold for the MGm response, was selected and test stimulation started. Once the MGm response appeared stable (approximately 20 min), 1–3 high frequency trains (100 or 300 Hz, 285 ms) were presented and test stimulation continued for approximately 60 min. Another set of stimulus–response curves was then generated and test stimulation resumed for up to 3 h after the train. In several animals, the pre-train test period was lengthened (40–60 min) to investigate the effects of the 0.2 Hz test stimulation. To complete testing, different stimulation frequencies were presented (2–500 Hz) to determine the frequency following characteristics of the MGm response. Throughout testing, animals were paralyzed (Flaxedil, i.v.; 10 mg/kg initial dose; 20 mg/h supplemental) and artificially respired.

Evoked responses, referenced to a skin flap, were recorded on magnetic tape and analyzed either on-line or off-line with an LSI-11 computer. Simple *t*-tests or one-way analyses of variance were used to determine significance of changes between pre- and post-train data samples. The present findings are for 10 animals with histologically verified electrode placements in the MGm and BIC, 2 of which also had a verified recording electrode in the inferior colliculus.

A typical MGm response to BIC stimulation

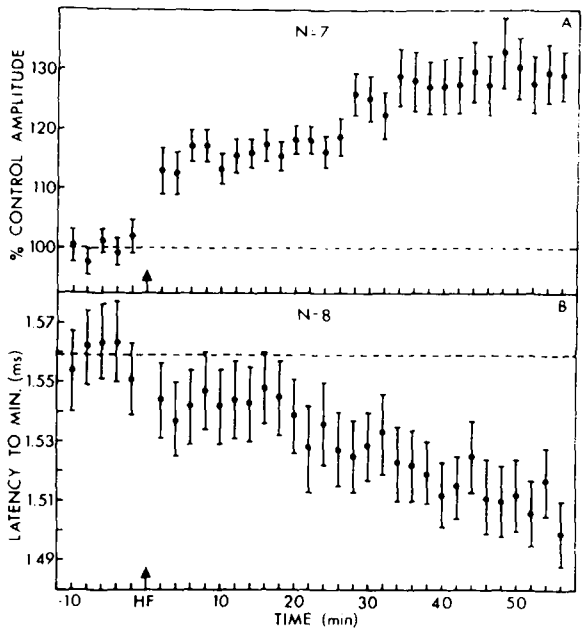

Fig. 2. The effects of high frequency (HF) stimulation on the MGm response to BIC stimulation. A: the amplitude of the MGm response, with respect to the pre-HF mean amplitude, is plotted versus time. Each point represents the averaged amplitude data from 7 out of 10 experiments in which HF related amplitude changes were observed. B: the latency-to-minimum (maximum negativity) of the MGm response is plotted versus time. Each point represents the averaged latency data from 8 out of 10 experiments in which HF related latency changes were observed and measurable. Vertical bars represent ± 1 standard error of the mean.

(Fig. 1B) consisted of a short duration negativity followed by a longer duration positivity. The maximum negativity had a mean latency of 1.56 ± 0.01 ms and ranged in size from 50 to 200 μV. The positivity was not present in all preparations, and was usually absent when the electrode was placed posteriorly in MGm. Consequently, the amplitude and latency of the maximum negativity were employed to characterize the MGm response. The stimulus artifact often partially obscured the BIC volley, making routine latency measurements of the volley impossible. However, when measurable, it preceded the maximum negativity of the MGm response by 0.7 0.9 ms. Also, the volley could follow stimulation frequencies over 500 Hz, whereas the MGm response often failed to follow 300 Hz stimulation. These observations suggest that the MGm response is a monosynaptic response.

During the pre-train test period, the amplitude and latency of the MGm response varied from one stimulus to the next. However, no significant ($P > 0.05$) increasing or decreasing trends in these measures were observed, even when this period was extended to 60 min. After the train, the amplitude and latency of the response changed. Initially, either a residual 'frequency facilitation'[10] or a slight depression of amplitude lasting from 30 s to 4 min was observed. In 7 out of 10 experiments, the amplitude of the MGm response then became significantly potentiated ($P < 0.005$), and this potentiation lasted at least 1 h after the high frequency train (Fig. 2A). In 6 cases, the amplitude was still potentiated (137.0 ± 11.7%) when recording was stopped 1.5 3.0 h (1.82 ± 0.16 h) after the train. The level of amplitude potentiation varied between experiments (118 201%), the mean level being 158.4 ± 12.8% of pre-train values. In 3 experiments, the amplitude of the MGm response remained unchanged ($P > 0.05$) from pre-train values for the duration of the post-train testing period. Interestingly, these were the only 3 instances where the MGm response failed to follow the train. These findings support the hypothesis that persistent increases in MGm response amplitude can be induced by repetitive activation of MGm synapses. Also, amplitude potentiation of the MGm response seems to be dependent upon synaptic transmission, which is the case for hippocampal LTP[7]. Further, it does not appear that tonic increases in the excitability of MGm neurons underlie the increased amplitudes. The spontaneous firing rate of these neurons does not change following a train which induces potentiation[8].

In 8 out of 10 experiments, a significant reduction ($P < 0.05$) in the latency of the MGm response was also observed following the high frequency train (Fig. 2B). The latency decreased steadily following the train, reaching a minimum after 30 50 min. In no instance did the latency return to the pre-train value by the end of testing. The maximum reduction in latency varied from 0.03 to 0.13 ms (0.08 ± 0.01 ms) across experiments. In the remaining 2 experiments, the latency also appeared to decrease after the

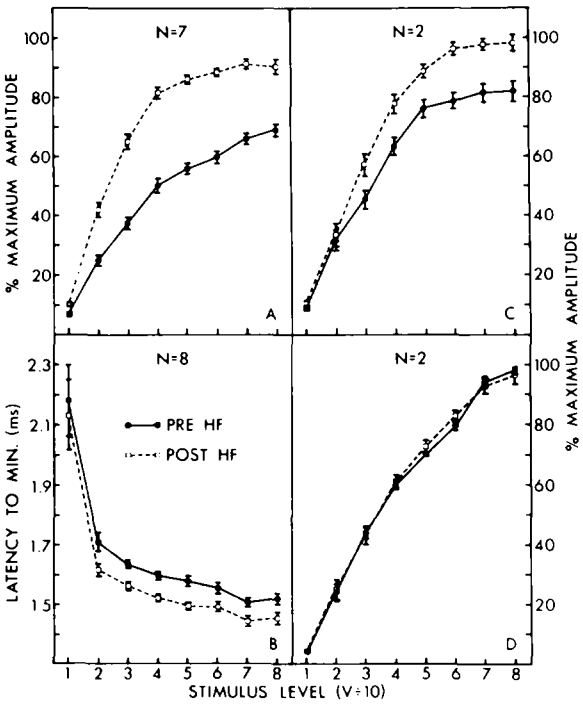

Fig. 3. The effects of high frequency (HF) stimulation on stimulus response curves. A and B: amplitude and latency-to-minimum curves for the MGm response to BIC stimulation as a function of stimulus level. The data represented in these curves are from the same experiments shown in Fig. 2, and were obtained 20 min before (●——●) and 60 min after (□-------□) HF stimulation. C and D: of the 7 subjects which developed amplitude potentiation, antidromic responses were recorded simultaneously in the IC in 2 cases. Their orthodromic and antidromic amplitude functions are given in C and D, respectively. Note the amplitude potentiation of the orthodromic response concurrent with the lack of change of the antidromic response. Stimulus level corresponds to current intensities of 0.1–0.8 mA.

train, but quantification was impossible because the latency could not be measured consistently. Of importance was the observation that the latency of the MGm response decreased after the train in all 3 experiments not showing amplitude potentiation. This suggests that the reduction in latency may be related to the repetitive activation of the presynaptic terminals, and that it is independent of the processes causing the increase in response amplitude.

Potentiation of response amplitude and reduction of response latency following the train were also observed in the stimulus response curves (Fig. 3A, B). After the train, the amplitude of the MGm response was significantly increased ($P < 0.005$), and the latency significantly decreased ($P < 0.01$), over the entire range of stimulus intensities, except at the lowest stimulus level where no differences ($P > 0.05$) were found. It was never possible to evoke a response before the train that was comparable in amplitude and latency to the maximally potentiated response. This suggests that the observed changes are not attributable to the recruitment of a previously subthreshold population of neurons, but more likely are due to an increase in the efficiency of existing synapses.

In 3 experiments the antidromic BIC volley invading the inferior colliculus was studied. No changes ($P > 0.05$) in the amplitude of the antidromic volley were observed following the train, even when the amplitude of the MGm response was significantly ($P < 0.05$) potentiated (Figs. 1C and 3C, D). Thus, the changes in the MGm response following the high frequency train are not caused by local changes at the site of stimulation.

In summary, these findings indicate that a region of the auditory system which develops rapid and persistent changes during behavioral conditioning also exhibits long-term potentiation. It now becomes pertinent to ask if these are closely related phenomena. Two lines of investigation should provide information on this point: first, can LTP be elicited in those subdivisions of the medial geniculate nucleus which are *not* modified by conditioning[1], and second, during conditioning episodes, do cells whose axons comprise the BIC fire at frequencies appropriate for the induction of LTP in the magnocellular medial geniculate nucleus?

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