Neuroscience Letters, 63 (1986) 76–80
Elsevier Scientific Publishers Ireland Ltd

NSL 03704

INHIBITION OF INFERIOR OLIVARY TRANSMISSION BY MESENCEPHALIC STIMULATION IN THE CAT

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(Received August 26th, 1985; Revised version received and accepted September 30th, 1985)

Key words: cerebellum – inferior olive – inhibition – cat

Cerebellar climbing fiber responses (CFRs) evoked in anesthetized cats by stimulation of peripheral nerves, contralateral inferior olive and cerebellar white matter were investigated by recording unit activity and surface field responses in anterior lobe of cerebellar cortex. When nerve and olive stimulation was preceded at long intervals (> 35 ms) by weak electrical stimulation of an ipsilateral mesencephalic area close to the locus coeruleus and brachium conjunctivum, CFRs could be virtually abolished in the pars intermedia but not in the vermis. White-matter evoked CFRs were not affected; thus the site of the inhibition was the inferior olive.

The cells of the inferior olive (IO), which project to the contralateral cerebellar cortex as climbing fibers, receive excitatory input through spinal pathways and descending pathways from the sensorimotor cortex. Inhibition of spino-olivary transmission by stimulation of the cerebral cortex has been demonstrated previously [8, 9], but it was not determined if this inhibition occurred in the IO or at a pre-olivary level. A recurrent inhibition of olivary cells has been demonstrated [2, 3] and also mutual inhibition between olivary cells projecting to adjacent cerebellar microzones [1]. The present investigation demonstrates that electrical stimulation of an area in the caudal mesencephalon (ME) produces a strong inhibition of cells in the contralateral IO.

The experiments were performed on 10 cats under deep pentobarbitone anesthesia (initial dose, 40 mg/kg, i.p.; additional doses of 5 mg/kg i.v. as required) and paralysed with gallamine triethiodide. The left (in two cases also part of the right) cerebellar anterior lobe and the inferior colliculus were exposed and covered with warm mineral oil. Climbing fiber responses (CFRs) were evoked by bipolar stimulation of the left superficial radial (SR) nerve by stimulation through a monopolar electrode inserted into the rostral part of the right dorsal accessory olive and by monopolar stimulation of the left subcortical cerebellar white matter. Monopolar tungsten electrodes were inserted vertically through the left inferior colliculus to a depth of 5–10 mm for ME stimulation. Unless otherwise stated, stimulation consisted of 3 shocks (0.2-ms square pulses at 100 Hz). Stimulation strength varied between 10 and 100 μA. Recordings from the cerebellar surface were made with silver ball electrodes and unitary recordings with 6–10 MΩ KCl-filled micropipettes. After each experiment, the cat brain was removed and the position of the ME electrodes checked by standard histological techniques.

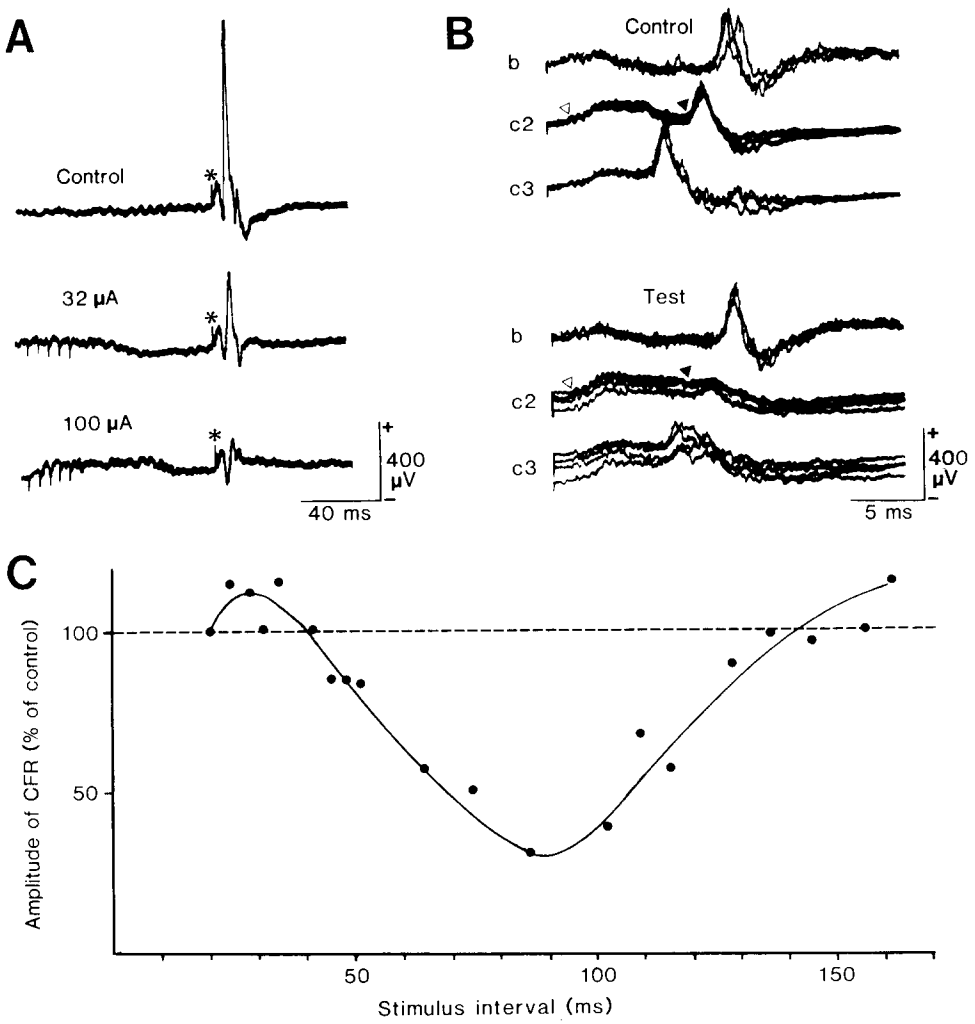

Fig. 1. Inhibition of CFRs by stimulation of ME. A: upper trace, CFRs recorded from cerebellar surface on stimulation of the IO (shock artefact indicated by asterisk). Middle and bottom traces, IO stimulation preceded by 5 shocks at 200 Hz to ME at 32 and 100 μA, respectively. B: top (control), superimposed traces of CFRs evoked by stimulation of SR nerve and recorded from b, c2 and c3 zones. Mossy fiber and climbing fiber responses in the c2 zone indicated by open and filled arrowheads, respectively. Bottom (test), SR stimulation preceded by ME stimulation. C: time-course of inhibition. Average amplitudes (n = 10–15) of CFRs (expressed as percent of control responses) plotted against ME to SR stimulus interval.

In the experiment illustrated in Fig. 1A, a CFR with stable amplitude was evoked by stimulation of the IO (control). CFRs are easily identified and distinguished from mossy fiber responses by their physiological properties [4]. The latency of the response (6.4 ms) indicates that it is evoked synaptically [4]. The amplitude of the CFR could be reliably reduced by preceding the IO stimulation at 100 ms with a train of pulses to the ME at 32 μA and virtually abolished when the strength of the ME stimulation was increased to 100 μA. CFRs evoked by stimulating climbing fibers directly

in the white matter were not inhibited. Thus, the site of the inhibition must be in the IO and not in the cerebellar cortex.

The effectiveness of the inhibition was strongly dependent on the number of conditioning shocks. For instance, in some cases where 3 shocks almost completely abolished the CFR, the inhibition was barely noticable with one shock, and this could not be compensated for completely by increasing stimulation strength. The frequency of the stimulus pulses to the ME was relatively unimportant. The effect was not very different when the frequency was increased from 100 to 330 Hz as long as the number of shocks was kept constant.

The effect of ME stimulation was studied in 3 physiologically identified zones in the anterior lobe. Fig. 1B shows records of CFRs and mossy fiber responses in the b, c2 and c3 zones (see references in ref. 11), evoked by stimulating the SR nerve. When nerve stimulation was preceded at 70 ms by ME stimulation, CFRs were strongly inhibited in the c2 and c3 zones but not in the b zone. No effect was observed on mossy fiber responses. In the two cats where recordings were made from the right cerebellar hemisphere after stimulation of the left ME, no inhibition was observed.

The latency of the inhibition varied between 35 and 50 ms, which is much longer than the few milliseconds reported for recurrent and mutual inhibition [1, 3]. It is noteworthy, however, that the mutual inhibition had two components, one of which had a latency of about 40 ms [1]. The duration was usually 100–120 ms, which is about the same as that reported for recurrent and for mutual inhibition. A complete time-course is shown for one case in Fig. 1C. In this case, the inhibition was preceded by a period of facilitation. This was often observed when the stimulation strength was supramaximal for inhibition but seldom occurred when inhibition was evoked with lower strengths.

A facilitation might suggest that the inhibition was due to a prior excitation of the IO and recurrent inhibition. However, no CFRs were observed as surface potentials as a result of ME stimulation (at the stimulation strengths employed here), and when unitary recordings were made, inhibition was often effective when the strength of the ME stimulation was well below the threshold for evoking CFRs. It is unlikely, although it cannot be excluded, that the stimulation activated neighbouring olivary cells, and that the inhibition observed was due to mutual inhibition of olivary cells.

The area from which inhibition could be produced was located below the inferior colliculus at depths between 6.5 and 8.5 mm and extended from 2.5 to 4.5 mm laterally. This is illustrated in Fig. 2A which shows a section of brainstem with 3 electrode tracks from one experiment, and in Fig. 2B, which shows the stimulus strength required for a 10% reduction of the CFR amplitude at different depths from the tracks shown in A. Inhibition was obtained rostrally to about AP0, where thresholds gradually increased. No caudal border could be determined. ME stimulation was tested to about P5, and the threshold for inhibition usually remained low (ca. 10 μA).

The effective area is close to the nucleus cuneiformis and to the mesencephalic locomotor region [5], and it corresponds well to the noradrenergic parabrachial nucleus and to the brachium conjunctivum. Assuming that the inhibition is produced by the noradrenaline system, there is a noradrenergic projection, presumably from the locus coeruleus or the parabrachial nucleus to the medial accessory olive [12] which sends climbing fibers to the c2 zone and to the rostral dorsal accessory olive

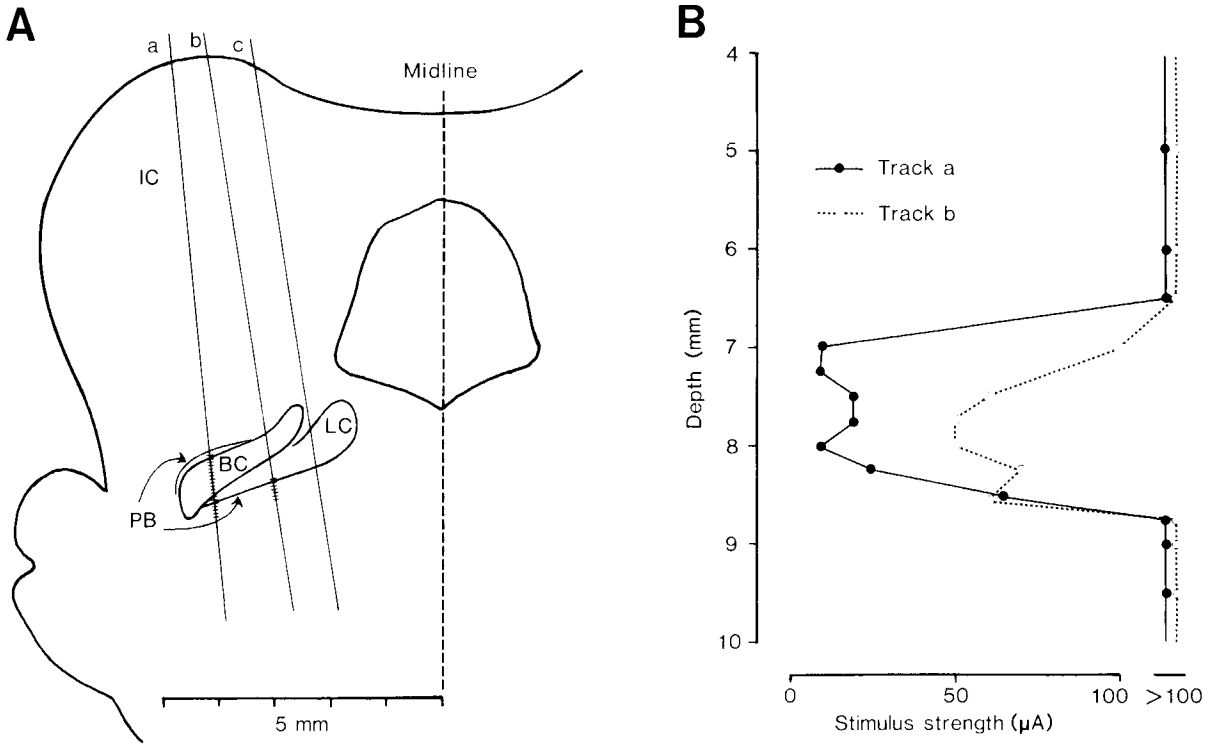

Fig. 2. Localization of inhibitory area. A: transverse section of the brainstem through caudal part of inferior colliculus. Three electrode tracks a, b and c, are shown. Depths from which inhibition could be produced at less than 50 μA indicated with crossed bars. BC, brachium conjunctivum; IC, inferior colliculus; LC, locus coeruleus; PB, parabrachial nucleus which surrounds BC. B: minimum stimulation strength required for 10% reduction of CFR amplitude versus depth of stimulation site. Track a: continuous line, filled circles; track b: interrupted line, open circles. No inhibition was obtained from track c at 100 μA.

which innervates the c3 zone [7]. The absence of inhibition in the b zone, which is innervated from the caudal dorsal accessory olive [6], would be consistent with the observation that this nucleus in the cat is very sparsely innervated by noradrenergic fibers [12, 14]. However, the noradrenergic system would not be expected to be strictly contralateral.

The brachium conjunctivum is known to contain fibers from the nucleus interpositus to the IO [13]. Recent evidence suggests the existence of a GABAergic projection from the interpositus nucleus to the IO [10]. Involvement of this projection in the inhibition would also explain the absence of effects on CFRs in the b zone, since there is no known projection through the brachium conjunctivum to the caudal part of the dorsal accessory olive [13]. A difficulty with this interpretation is the very long latency of the inhibition. The mechanisms of the inhibition are presently being investigated.

This work was supported by grants from the Medical Faculty, University of Lund, and to Dr. O. Oscarsson from the Swedish Medical Research Council (Project No. 010013). The author wishes to thank Dr. Norma C. Campbell for participation in some of the experiments and Dr. Leif Wiklund for assistance with the histology.

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