Exp Brain Res (1988) 72: 450–456

Experimental Brain Research

Evidence for a GABA-mediated cerebellar inhibition of the inferior olive in the cat

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Summary. 1. Climbing fibres were activated by peripheral nerve stimulation at 'high' frequencies (> 3 Hz) for 15–25 s and then at 0.9 Hz for about 1 min. The high frequency activation induced a post-conditioning inhibition, lasting up to about 1 min, of climbing fibre responses recorded from the cerebellar surface. 2. Electrolytic lesions were made in the superior cerebellar peduncle (brachium conjunctivum). After the lesion, the post-conditioning inhibition was completely eliminated. 3. Injections of the GABA-receptor blocker bicuculline methiodide into the inferior olive reversibly blocked the post-conditioning inhibition. 4. The results support the hypothesis proposed by Andersson and Hesslow (1987a), that post-conditioning inhibition is mediated by a GABA-ergic interposito-olivary pathway.

Key words: Cerebellum – Inferior olive – Interposito-olivary pathway – Brachium conjunctivum – GABA

Introduction

It was recently shown by Andersson and Hesslow (1987a) that activation of climbing fibres at high frequencies leads to a strong depression of inferior olive excitability. In these experiments, climbing fibre responses (CFRs) were recorded from the surface of the cerebellar anterior lobe, mainly in the c1 and c3 zones (Oscarsson 1980), in response to peripheral nerve stimulation at two different frequencies. First, during a conditioning period, the nerve was stimulated for 15–25 s at > 3 Hz. This was followed by a test period during which the nerve was stimulated at 0.9 Hz for about one minute. Typically, the CFR amplitudes during the conditioning period were similar to those during a previous control stimulation at 0.9 Hz. However, during the test period, the CFRs were strongly depressed for up to one minute. Examples of this phenomenon are shown in Figs. 1D and 3A of the present paper.

It was suggested that this depression was due to activation of the GABA-ergic, presumably inhibitory, pathway from the interpositus nucleus to the inferior olive reported by Nelson et al. (1984). Rawson and Tilokskulchai (1981) reported that high frequency climbing fibre activation can induce a suppression of the simple spike firing of Purkinje cells. This would lead to a disinhibition of the nucleo-olivary neurones, which would, in turn, depress the inferior olive. In a study of cerebellar unit activity after such high frequency climbing fibre activation, the behaviour of both Purkinje cells and interposito-olivary neurones was consistent with this hypothesis (Andersson and Hesslow 1987b).

The experiments reported in the present study were designed to test this hypothesis further. If the post-conditioning inhibition of inferior olive excitability is mediated by the nucleo-olivary projection, it should be eliminated by lesions of the brachium conjunctivum, in which the interposito-olivary fibres travel (Graybiel et al. 1973; Tolbert et al. 1976). Furthermore, since this pathway is GABA-ergic, application of a GABA-receptor blocking agent such as bicuculline to the inferior olive would be expected to block the post-conditioning inhibition.

Preliminary communications have been published (Andersson and Hesslow 1986; Andersson et al. 1987).

Methods

The experiments were performed on 9 cats (2.5–4.3 kg). Six of these were deeply anaesthetized with pentobarbitone (initial dose 40 mg/kg intraperitoneally; supplementary doses of 5 mg intravenously as required). The level of anaesthesia was adjusted such that the pupils were maximally constricted.

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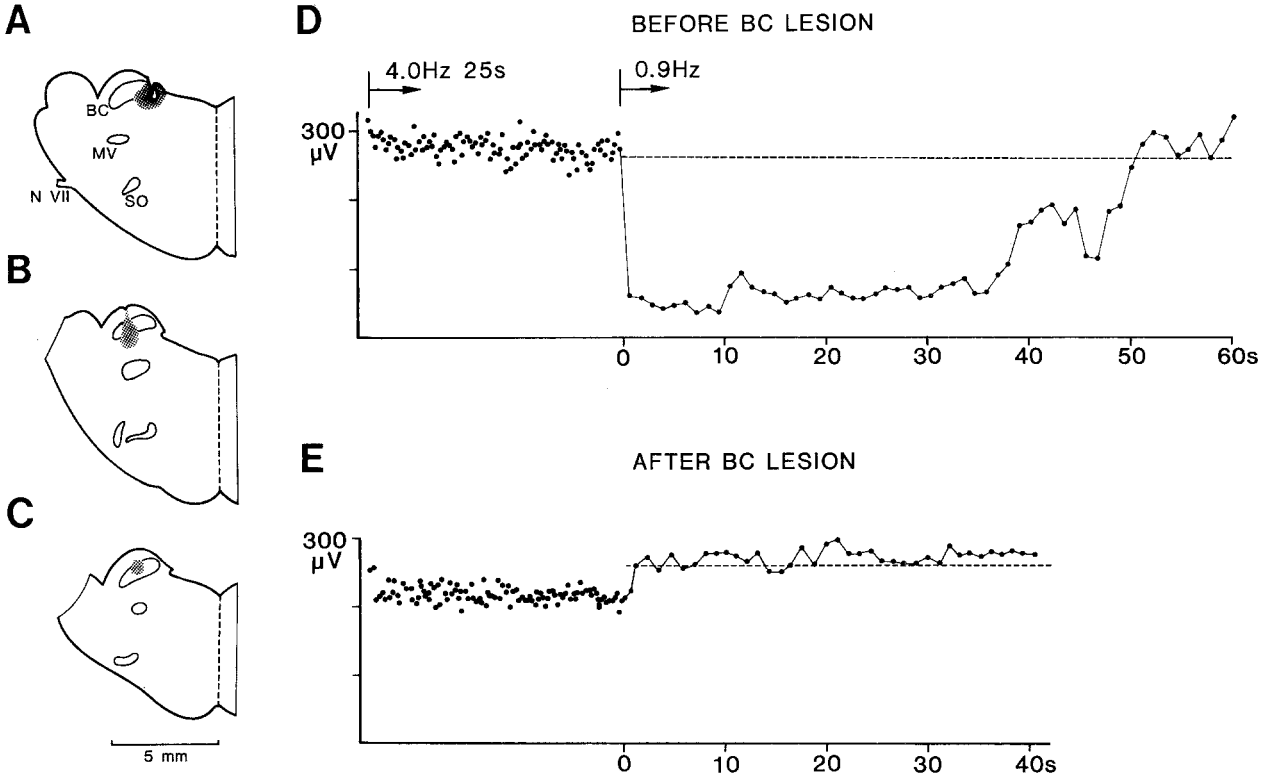

Fig. 1. A–C Electrolytic lesions of the brachium conjunctivum. Transverse sections of the brain stems of 3 cats. Rostrocaudal level P 3.5–4.5 mm. BC: brachium conjunctivum, NVII: 7th nerve, SO: superior olive, MV: motor nucleus of the 5th nerve. The shaded areas indicate extents of visible tissue damage. **D–E** Effect of high frequency climbing fibre activation before (**D**) and after (**E**) lesion of the BC. Left sciatic nerve stimulated at 4.0 Hz for 25 s and thereafter at 0.9 Hz. Dots indicate amplitudes of climbing fibre responses recorded from the surface of the c1 zone. Interrupted line shows control level of climbing fibre response amplitude obtained before the test at 0.9 Hz stimulation

In 3 of the barbiturate anaesthetized cats, electrolytic lesions were made in the brachium conjunctivum by passing a 0.5–1.5 mA direct current through the tip of a tungsten electrode for 30–120 s. The brains of these cats were saved for routine histological examination (cresyl violet).

In 3 other barbiturate anaesthetized cats, the ventral aspect of the brain stem was exposed in order to permit insertion of electrodes and micropipettes into the inferior olive. These cats were mounted sideways to permit access to both the cerebellum and the ventral brain stem. Injections of 0.3–0.8 μl of 2.0 mM bicuculline methiodide (Sigma) dissolved in Ringer solution were made into the inferior olive. The solution was injected through a glass micropipette fastened to a Hamilton syringe.

The remaining 3 cats were decerebrated at the precollicular level under halothane anaesthesia, which was allowed to wear off after the operation. Just prior to the trials described in this paper, 10–20 mg of pentobarbitone was given intravenously.

All the animals were paralyzed with gallamine triethiodide and artificially ventilated. The end-expiratory CO_2 concentration, arterial blood pressure and rectal temperature were continuously monitored and kept within physiological limits.

The left anterior lobe of the cerebellum was exposed and the cortex was covered with warm mineral oil. The left common or superficial radial nerve and the left sciatic nerve were dissected and mounted for stimulation.

CFRs were evoked by bipolar stimulation of limb nerves, with square pulses of 100 μs duration. Stimulation strength was slightly above that which evoked a maximal CFR. Recordings from the cerebellar surface were made with silver ball electrodes. The reference electrode was placed in the neck musculature. All recordings were made in the c1 and c3 zones of the pars intermedia of the anterior lobe.

Results

Lesions of the brachium conjunctivum

After a number of initial control trials, in which the parameters of the conditioning stimulation were varied, electrolytic lesions were made in the left brachium conjunctivum (BC) in 3 cats. Histological reconstructions of these lesions are shown in Fig. 1A–C. The shaded areas correspond to the maximal extent of visible tissue damage. The lesion electrodes were placed at rostro-caudal levels P 3.5–4.5 mm (cf. Berman 1968). All three lesions clearly destroyed part of the left brachium conjunctivum. One of them (A) destroyed the medial part of the BC and some of the surrounding tissue, whereas the other two lesions (B–C) mainly involved the center of the BC with slight damage to surrounding tissue.

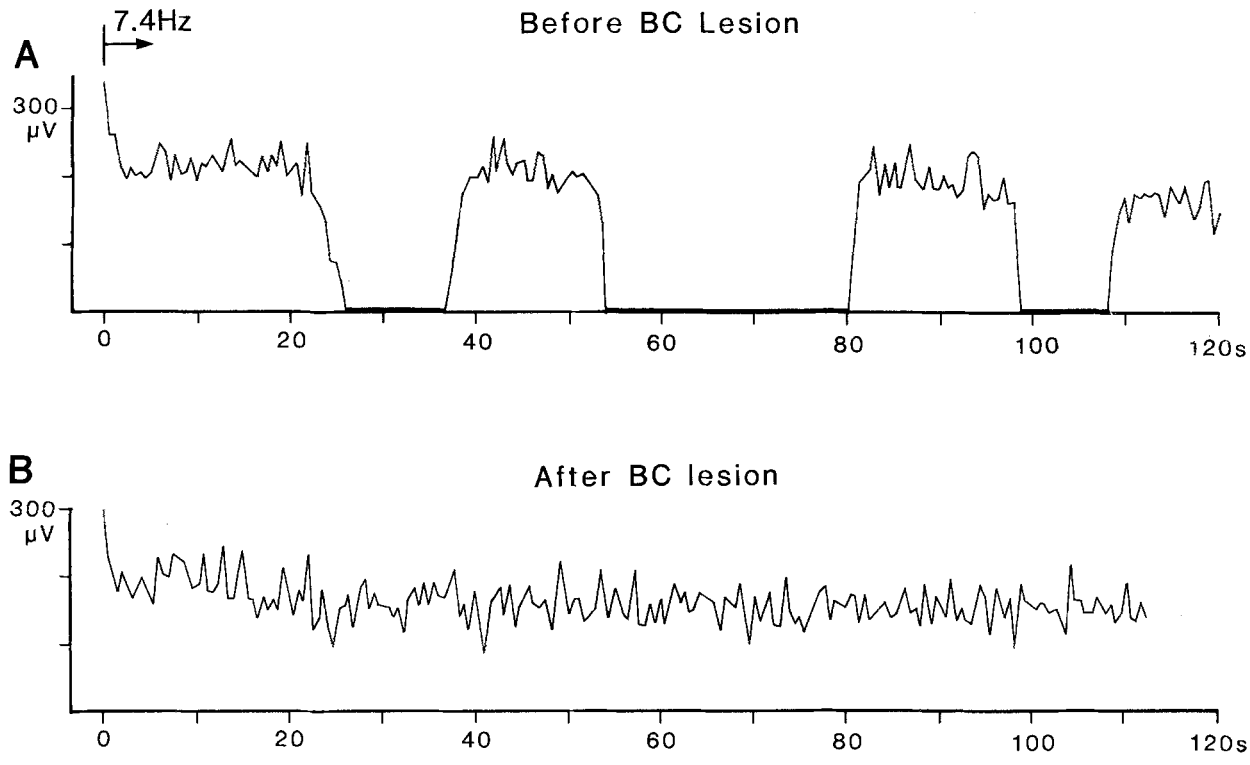

Fig. 2A, B. Climbing fibre response amplitude during long-lasting high frequency climbing fibre activation. Climbing fibres were activated by 7.4 Hz stimulation of the sciatic nerve and responses were recorded from the c1 zone. **A** Before lesion. **B** After lesion of BC (same as in 1A)

Figure 1D–E shows the effect of the lesion illustrated in A. The curve in D shows a control trial prior to the lesion. CFRs were evoked by stimulation of the sciatic nerve and recorded in the c1 zone. Each dot corresponds to a single CFR. The interrupted line indicates the average control amplitude of the CFRs when stimulated at 0.9 Hz. The conditioning stimulation had a frequency of 4.0 Hz and a duration of 25 s, which was well above the threshold for inducing a strong depression of the inferior olive. The CFRs had a stable amplitude, similar to the control level, during the conditioning period and were strongly suppressed for about 50 s afterwards. Figure 1E shows the corresponding curve obtained after an electrolytic lesion of the BC (1.5 mA for 70 s). In this example, the amplitudes of the CFRs were slightly depressed during the conditioning stimulation. More importantly, there was no depression of the CFRs after the conditioning period.

In this experiment, smaller lesions were initially made with currents of 0.5 and 1.0 mA for 60 s. These lesions only produced small and transient effects. The larger lesion described above had to be made in order to produce the effect illustrated in Fig. 1E. This indicates that smaller lesions, which were centered outside the BC, had no effect.

After this lesion, it was impossible to produce any depression even when the duration and frequency of the conditioning stimulation were increased up to 7.4 Hz for 100 s. Similar results were obtained in the other two animals with the lesions shown in Fig. 1B and C.

There is little overlap between the lesions shown in Fig. 1A–C. It is likely, however, that conduction was blocked in areas which were larger than the histologically identified lesions. Such functional lesions would overlap in the BC, and would account for the fact that they had identical effects.

Decerebrate animals

It has been shown that stimulation of the cerebral cortex can inhibit peripherally evoked climbing fibre responses in the cerebellar cortex (Leicht et al. 1972; Rowe 1977). In order to exclude the possibility that the post-conditioning inhibition of the inferior olive involved cortical structures, trials with high frequency climbing fibre activation were made in 3 decerebrate cats. The results were similar to those obtained in animals with intact brain stems.

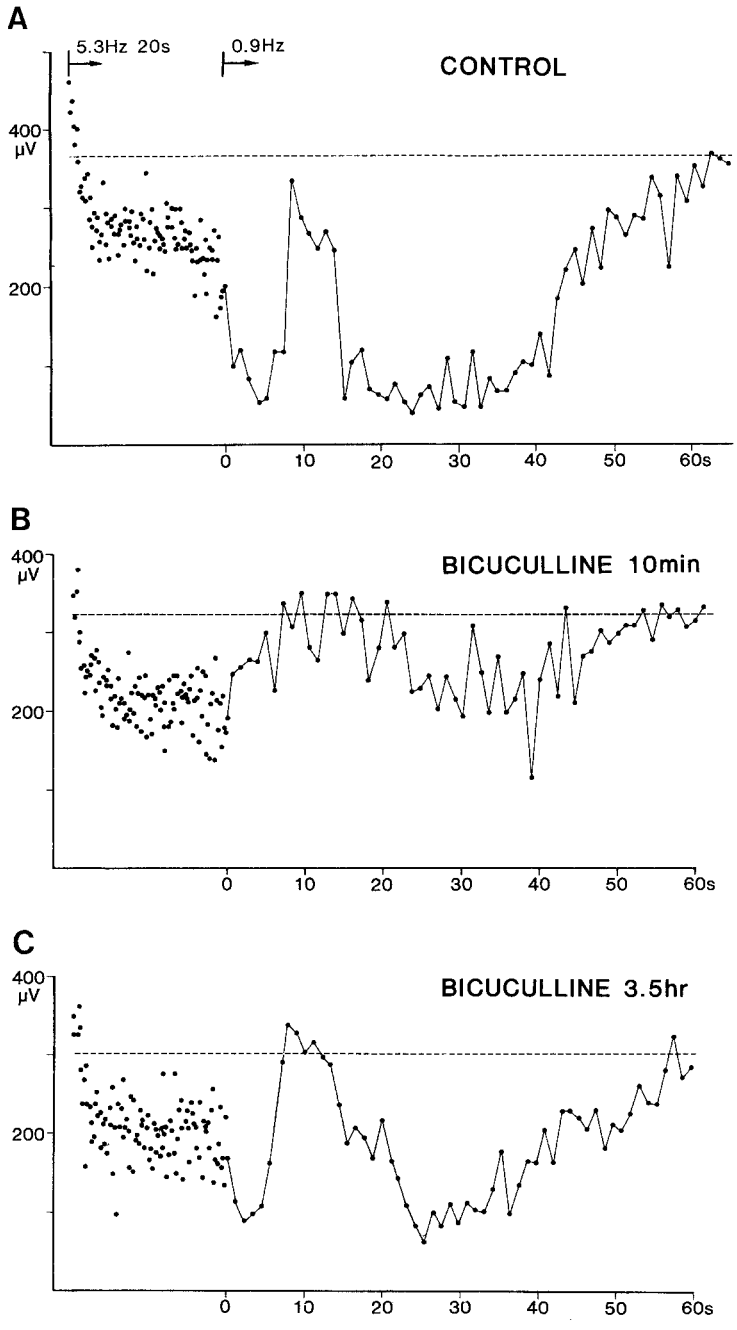

Fig. 3A–C. Effect of high frequency climbing fibre activation before and after injection of 0.8 μl of 2.0 mM bicuculline into the inferior olive. Stimulation of superficial radial nerve at 5.3 Hz for 20 s and at 0.9 Hz for 60 s. Recording in c3 zone. **A** Before injection. **B** 10 min after injection. **C** 3.5 h after injection

Longlasting high frequency stimulation

Miller and Oscarsson (1970) described a phenomenon which is interesting in relation to the post-conditioning inhibition. They evoked CFRs in a single Purkinje cell by stimulating a peripheral nerve continuously at frequencies of 1–50 Hz. At frequencies above 5 Hz, the response probability of the Purkinje cell was found to alternate between periods where each stimulus was followed by a CFR and periods of complete absence of the CFRs. Since this phenomenon might involve mechanisms similar to those suggested for the more short-lasting high frequency stimulation, we tested the effects of long-lasting stimulation before and after a lesion of the BC.

The results from one experiment are illustrated in Fig. 2. The ipsilateral sciatic nerve was stimulated at 7.4 Hz and CFRs were recorded in the c1 zone. The diagram in A shows the amplitude of every fourth CFR during such stimulation before the BC lesion. The response amplitudes varied in an on-off manner.

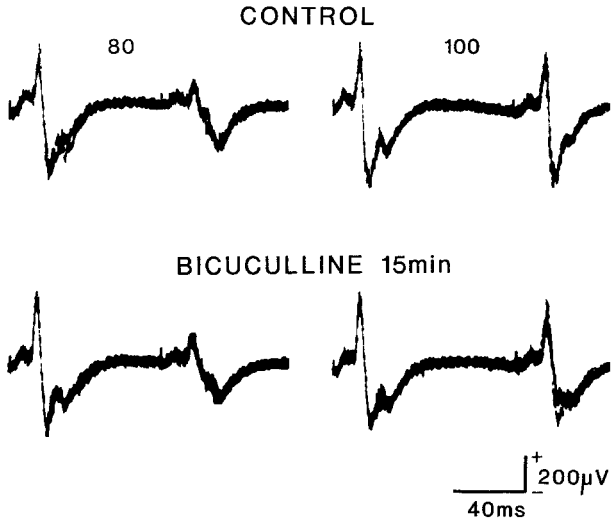

Fig. 4. Recordings of CFR's from cerebellar surface, illustrating recurrent inhibition of inferior olive before and after injections of bicuculline. Stimulation of ipsilateral superficial radial nerve at 80 and 100 ms intervals

Initially, the CFRs followed the stimulation with high amplitudes, but after about 20 s the responses disappeared completely for about 15 s and then returned again with high amplitudes. The diagram in Fig. 2B was obtained with a similar stimulation after the BC lesion (Fig. 1A). The CFR amplitudes varied, but there were no on-off periods.

Bicuculline injections

In these experiments, the rostral dorsal accessory olive was first localized by stimulating various parts of the inferior olive and recording CFRs from the c1 or c3 zone. A micropipette was then inserted into the area from which CFRs could be evoked at low threshold and 0.3–0.8 μl of 2 mM bicuculline methiodide was injected. The results of one of these experiments are illustrated in Fig. 3.

Figure 3A shows the result of high frequency conditioning stimulation before the injection. In this case, CFRs were evoked by stimulation of the superficial radial nerve and recorded from the c3 zone of the anterior lobe. The conditioning stimulation had a frequency of 5.3 Hz and a duration of 20 s. These parameters were chosen to ensure that the conditioning stimulation was well above the threshold for inducing a strong depression. The CFRs had difficulty in following this frequency, and thus the amplitudes were reduced from a control level of 360 μV to about 200 μV. After the conditioning stimulation, the CFR amplitude was strongly reduced for about 60 s with a brief recovery about 10 s into the test period (cf. Andersson and Hesslow 1987a).

Similar conditioning tests were made immediately after injection of 0.3 μl of bicuculline, and at various intervals up to 3.5 h later. Figure 3B shows the result of such a test 10 min after the injection. The behaviour of the CFRs during the conditioning period was similar to that in the control case. However, after the conditioning stimulation, the CFR amplitudes returned to the control level. The small depression of the CFRs between 20 and 60 s during the test period was much weaker than that obtained before the bicuculline injection.

The effect of the bicuculline injection gradually declined over a period of a few hours. Figure 3C shows a trial conducted about 3.5 h after the injection. Although not quite as strong as in the control trial, a clear post-conditioning inhibition was again present.

The bicuculline injections had no effect on the thresholds or amplitudes of the CFRs. Recurrent inhibition (Armstrong and Harvey 1966; Armstrong et al. 1968) of CFRs was also studied before and after the injections, but there was no difference either in the strength or in the time course of recurrent inhibition. This is shown in Fig. 4. Two CFRs were evoked by stimulation of the superficial radial nerve at varying intervals. Figure 4 shows CFRs at two different intervals (80 ms and 100 ms) before the bicuculline injection (control). The second response was depressed at 80 ms, and there was a partial recovery at 100 ms (cf. Armstrong and Harvey 1966; Armstrong et al. 1968). The records in the lower row are from similar tests after the injection of bicuculline. The results were identical.

The fact that bicuculline had no effect on recurrent inhibition in the inferior olive is consistent with the suggestion that this phenomenon is not mediated by inhibitory interneurones but by membrane properties of the olivary cells (Llinás and Yarom 1981a, b).

Discussion

Andersson and Hesslow (1987a) suggested that the post-conditioning inhibition is due to the activation of an inhibitory interposito-olivary pathway (cf. Nelson et al. 1984). This hypothesis fits well with the depression of simple spike firing that follows high frequency climbing fibre activation (Rawson and Tilokskulchai 1981; Andersson and Hesslow 1987b). It also fits with the activation found in interposito-olivary cells (Andersson and Hesslow 1987b).

The present results lend further support to this interpretation. Small lesions of the BC completely abolished the effects of high frequency climbing fibre activation on inferior olive excitability. Since the lesions also eliminated the on-off alternations in inferior olive excitability described by Miller and Oscarsson (1970), it appears that these alternations also depend on cerebellar output. The results do not, of course, exclude the possibility that some circuit other than the nucleo-olivary pathway is involved. However, precollicular decerebration had no effect. Although some brain stem system might mediate the inhibition, the nucleo-olivary pathway is the simplest explanation.

Injections of the GABA-receptor blocker bicuculline resulted in a strongly reduced post-conditioning inhibition. This is also in agreement with the hypothesis of a GABA-ergic inhibition. Together with the previously reported findings (Andersson and Hesslow 1987a, b), these results strongly suggest that the cerebellum contributes to the control of inferior olive excitability through a GABA-ergic mechanism. The interposito-olivary pathway is a likely candidate for the mediation of this effect (Nelson et al. 1984).

Possible functions of the nucleo-olivary inhibition

The climbing fibre input to the Purkinje cells has both a short-term excitatory and a tonic inhibitory effect (Eccles et al. 1967; Colin et al. 1980; Montarolo et al. 1982). Complex spikes in Purkinje cells produce inhibition in the interposito-olivary cells. Since the excitation provided by the climbing fibre collaterals to the nuclei is relatively weak (cf. Andersson and Oscarsson 1978), the net short-term effect would be a depression of the nuclear cells which would disinhibit the olive. With respect to this Purkinje cell excitation, an inhibitory nucleo-olivary pathway would thus function as a positive feedback system. This is, however, very improbable.

It is more likely that the nucleo-olivary pathway is part of a negative feedback system. It has been shown that the climbing fibres exert a tonic inhibitory control of the Purkinje cell simple spike firing rate (Colin et al. 1980; Montarolo et al. 1982). With respect to this effect, the nucleo-olivary pathway would provide negative feed-back information to the inferior olive and contribute to the control of the overall simple spike discharge of the Purkinje cells.

A second suggestion pertains to the possibility that the parallel fibre-Purkinje cell synapses are sites of motor learning. It was suggested by Albus (1971) and there is now strong empirical support for this theory (Ito et al. 1982; Ekerot and Kano 1985), that the climbing fibre input tends to depress those parallel fibre synapses which have just been active. In order to ensure that the magnitude of this depression is appropriate, a feedback loop might be important.

Such a feed-back mechanism could explain the blocking phenomenon in classical conditioning (Kamin 1967). When a motor response has been firmly conditioned to one stimulus, for example a tone, and a second conditioned stimulus, for example a light, is then presented simultaneously with the tone, conditioning to the second stimulus is very inefficient. If instead, only the second conditioned stimulus is paired with the unconditioned stimulus, conditioning proceeds normally. There is now good evidence that the cerebellum is essential for classical conditioning of the eye-blink response in rabbits when the conditioned stimulus is either a tone or a light and the unconditioned stimulus is an air puff to the cornea or a periorbital electrical stimulation (McCormick et al. 1982; Yeo et al. 1985a, b). Recent results also suggest that the conditioned stimulus, i.e. tone or light, reaches the cerebellum via the mossy fibre-parallel fibre system, while the unconditioned stimulus activates climbing fibres (Yeo et al. 1985c). If, as reported by McCormick and Thompson (1984), the interpositus discharge increases in response to a firmly conditioned stimulus in advance of the unconditioned stimulus, the inferior olivary cells will be inhibited at the time of the unconditioned stimulus. Thus, if a second conditioned stimulus is added, this will not be followed by climbing fibre activation. If the climbing fibres in such a system function as a teaching line, further conditioning will then be prevented.

A third possibility, not incompatible with the previous suggestions, is that the nucleo-olivary pathway is involved in the gating of olivary transmission. According to the "error signal" hypothesis (see Oscarsson 1980; Ito 1984), the climbing fibres signal to the cerebellar cortex that some movement has been or is being incorrectly performed. There are some empirical findings which lend support to this hypothesis. For instance, climbing fibres discharge in response to passive tactile stimulation of the paw, but not when similar stimulation results from an active movement and thus is "expected" by the organism (Armstrong et al. 1982; Gellman et al. 1985; cf. also Andersson and Armstrong 1987). There is no information to date about which mechanisms might be responsible for the suppression of the olivary discharge during active movements or even if such a depression takes place in the inferior olive. The nucleo-olivary projection might play a role in this gating when the cerebellum is involved in the control of the movement.

Sotelo et al. (1986) reported an association between the GAD-positive synaptic terminals and dendritic gap junctions in the inferior olive, suggesting that GABA might modulate electrotonic coupling of olivary neurones, rather than exert a classical inhibitory effect. The findings, described above, of a strong inhibition of the inferior olive do not necessarily exclude such a mechanism. The high frequency climbing fibre activation employed in the present

experiments produces a very strong activation of the interposito-olivary cells (Andersson and Hesslow 1987b). It is possible, therefore, that these experiments are not well suited for revealing more subtle effects on the inferior olivary neurones.

Acknowledgements. This work was supported by grants from the Medical Faculty, University of Lund, and from the Swedish Medical Research Council (project nos. 01013 and K86-04P-7003-03).

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Received November 18, 1987 / Accepted March 28, 1988