

REVIEW ARTICLE

Cerebellar control of the inferior olive

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Abstract

A subpopulation of neurones in the cerebellar nuclei projects to the inferior olive, the source of the climbing fibre input to the cerebellum. This nucleo-olivary projection follows the zonal and, probably also, the microzonal arrangement of the cerebellum so that closed loops are formed between the neurones in the olive, the cerebellar cortex and the nuclei. The nucleo-olivary pathway is GABAergic, but several investigators argue that its main effect is to regulate electrotonic coupling between cells in the inferior olive rather than inhibit the olive. However, there is now strong evidence that the nucleo-olivary fibres do inhibit the olive. Three functions have been suggested for this inhibition: (i) feedback control of background activity in Purkinje cells, (ii) feedback control of learning, and (iii) gating of olivary input in general. Evidence is consistent with (i) and (ii). Activity in the nucleo-olivary pathway suppresses both synaptic transmission and background activity in the olive. When learned blink responses develop, the blink related part of the olive is inhibited while blinks are produced. When the nucleo-olivary pathway is interrupted, there is a corresponding increase in complex spike discharge in Purkinje cells followed by a strong suppression of simple spike firing. Stimulation of the pathway has the opposite results. It is concluded that the nucleo-olivary fibres are inhibitory and that they form a number of independent feedback loops, each one specific for a microcomplex, that regulate cerebellar learning as well as spontaneous activity in the olivo-cerebellar circuit.

Key words: *Purkinje cell, cerebellar nuclei, inferior olive, climbing fibre, nucleo-olivary*

Introduction

Climbing fibres, originating in the inferior olive contact Purkinje cells and interneurons in the cerebellar cortex as well as cells in the cerebellar nuclei. The nuclei project to the cerebral cortex via the thalamus and to various motor nuclei in the brain stem but also to the inferior olive, thus forming an olivo-cerebello-olivary loop (Figure 1) (1–3). When this nucleo-olivary (NO) projection was first demonstrated (see (4) for a detailed review), it was believed to consist of collaterals of other outward projecting nuclear neurones (5) and it was generally assumed that the NO projection was excitatory (6,7). It was therefore surprising when it was discovered independently that electrical stimulation of the NO fibres caused a strong inhibition of the inferior olive (8) and that the olive projecting neurones are GABA-ergic (9). These findings suggested that the NO fibres are inhibitory rather than excitatory and that they are part of a negative feedback loop for controlling cerebellar function (10). In this review, we will summarize some recent work on the NO pathway focusing on its functional significance.

Anatomical organization of the NO pathway

Several studies have shown that the NO fibres originate in a subpopulation of small (<20 μm) cells in the cerebellar nuclei (2,11) and that they send thin (1–2 μm) axons to the contralateral inferior olive (3,12) although, in the rat, there also seems to be a weaker ipsilateral projection (13). The NO fibres make synaptic contacts mainly with the dendrites of the olivary neurones and it has been reported that cerebello-olivary fibres often synapse near gap junctions (14–16). It was initially unclear if the NO fibres were collaterals of the ascending fibres in the brachium conjunctivum (superior cerebellar peduncle) or a separate population (1,5,11,17). However, at least in the cat, it has been shown that the pathway runs as separate fibres ventral to the brachium conjunctivum and that they cross at the same level as the fibres from the brachium (2). This is also consistent with physiological evidence from ferrets (18).

As far as is known, the topography of the NO projection matches the olivo-cortical projection (19). Those parts of the olive that project to a certain

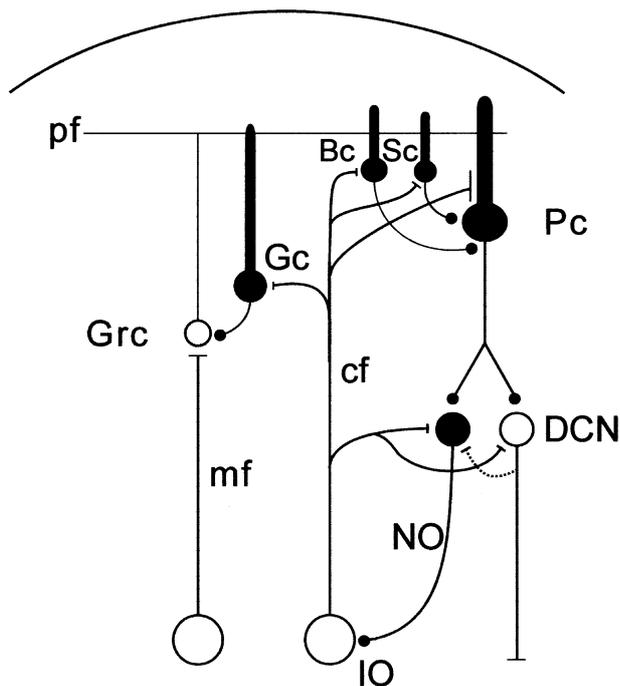


Figure 1. Wiring diagram of the cerebellar cortex and the cerebellar nuclei. Bc, Basket cell; DCN, Deep cerebellar nuclei; cf, climbing fibre; Gc, Golgi cell; Grc, Granule cell; IO, Inferior olive; mf, mossy fibre; NO, Nucleo-olivary pathway; Pc, Purkinje cell; pf, parallel fibre; Sc, Stellate cell.

cortical zone receive input from the cerebellar nucleus controlled by that zone (4,12). For instance, the rostral part of the dorsal accessory olive (DAO) projects to the C1 and C3 zones, which control the anterior interpositus nucleus that projects back to the rostral DAO. There is a similar loop between the medial accessory olive, the C2 zone and the posterior interpositus nucleus and between the principal olive, the D zone and the dentate nucleus.

This organizational principle seems to apply also at the level of the microzonal structure of the cerebellum. Andersson and Oscarsson (20) suggested that the microzone, a parasagittal strip of Purkinje cells with a common climbing fibre input, was the functional unit of the cerebellar cortex. It extended this concept to the *microcomplex*, which included not only the Purkinje cells of a microzone but also target neurones in the cerebellar nuclei and the olivary cells providing input to the microzone and the corresponding group of nuclear cells (6,21). Both physiological and anatomical evidence suggests that the nucleo-olivary neurones project specifically to olivary neurones in, or at least close to, the same microcomplex (22,23). For instance, during recordings from Purkinje cells in microcomplexes activated by radial versus ulnar nerve stimulation, NO inhibition of one microcomplex had no effect on the other one (22). A schematic diagram of the full cerebellar microcomplex is shown in Figure 1.

It is still not entirely clear what determines the activity of the NO neurones, if they are spontaneously active and what their input is. There is

anatomical evidence that they are controlled by Purkinje cells (24). However, there is also evidence that NO neurones may be driven by collaterals of other nuclear cells. When tracking and stimulating the area around the brachium conjunctivum, we found two discrete sites from which the olive could be inhibited, one just below the brachium conjunctivum, where the NO fibres travel, and one within the brachium (18). The effects of stimulating these two sites were indistinguishable, suggesting that they activated a common mechanism. This could most easily be explained if there were collaterals from the excitatory outward projecting nuclear neurones to the olive projecting neurones, so that stimulation of the brachium conjunctivum would cause antidromic activation of outgoing fibres and excitation of NO neurones via the collaterals.

Inhibitory nature of the NO pathway

Direct electrical stimulation in, or close to, the brachium conjunctivum in cats was shown to cause a strong inhibition of transmission in the inferior olive (8). Similar results were later obtained from ferrets (18) (Figure 2A) and stimulating the nuclei in rats was also found to inhibit the inferior olive (25).

The first studies in cats revealed an inhibition with extremely long latency (> 35 ms). This initially cast some doubt on the interpretation that the inhibition was really a monosynaptic effect mediated by the NO fibres. However, other physiological evidence later confirmed the inhibitory nature of the pathway. High frequency activation of the inferior olive, followed by low frequency stimulation, resulted in a strong depression of olivary responding during the low frequency stimulation period (26). It was suggested that this phenomenon occurred because the initial high frequency climbing fibre activation reduced Purkinje cell simple spike firing. This would in turn release the cerebellar nuclei from Purkinje cell inhibition and, as a consequence, inhibit the inferior olive. This suggestion was confirmed by unit recordings from Purkinje cells and neurones in the anterior interpositus nucleus (27). Furthermore, it was shown that the depression of the olive disappeared if the NO pathway was interrupted by lesions or if small amounts of the GABA-blocker bicuculline was injected into the inferior olive (10). Recent experiments have shown that blocking NO transmission (28) also increases the spontaneous output from the olive as does injection of a GABA antagonist into the inferior olive (29).

Of course, the inhibitory nature of the NO pathway has also been suggested by anatomical data. Several studies have shown that the synapses of the NO neurones in the olive are symmetrical and contain pleiomorphic vesicles (14,30,31) indicating that the pathway is inhibitory. In agreement with these findings, it has also been shown that the

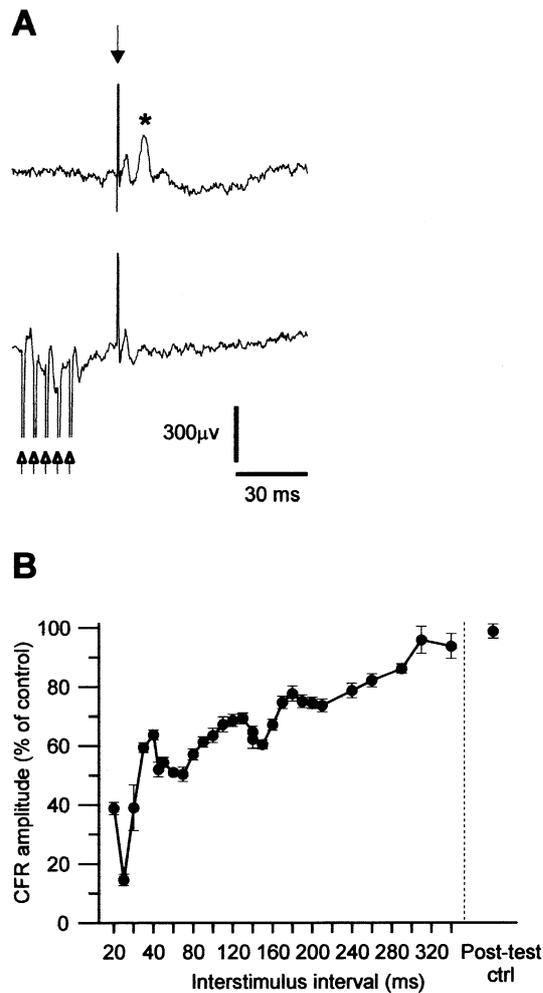


Figure 2. Effect of stimulation of the nucleo-olivary pathway on climbing fibre activity in the cerebellar cortex. (A) Example of the depression of a climbing fibre response (CFR), recorded from the surface of the cerebellar cortex, after stimulation of the nucleo-olivary pathway. In the upper trace, the periorbital stimulus pulse (filled arrow indicates stimulation artefact) elicits a characteristic mossy fibre response and a CFR (indicated by an asterisk). In the lower trace, the periorbital stimulus is preceded by a stimulus train (indicated by open arrows) (5 pulses, 200 Hz) delivered to the nucleo-olivary pathway. (B) Time course of the CFR inhibition after stimulation of the nucleo-olivary pathway. Amplitude of CFRs elicited by periorbital stimulation at different times after nucleo-olivary stimulation onset. Nucleo-olivary stimulation consisted of a train of pulses as indicated in A. CFR depression up to 340 ms after the stimulation. Mean \pm SEM of 10 consecutive trials. (Figure 2B adapted from ref. 18.)

olive-projecting neurones are GAD positive (that is, they contain the GABA-synthesizing enzyme glutamic acid decarboxylase) and thus they are GABAergic (9,31).

The long latency of the inhibition elicited by direct stimulation of NO fibres is enigmatic. In ferrets, the peak inhibition in the inferior olive occurs after about 30 ms with an onset latency between 15 and 25 ms (Figure 2B) (35–50 ms in the cat) (8,18). However, shorter latencies (2.6–6.4 ms) for the inhibition have been reported from investigations in the anaesthetized rat (25). In the latter study the

inhibition was evoked by stimulation of the contralateral lateral cerebellar nucleus.

Although the NO fibres are thin, this can hardly explain the long latency. Antidromic activation of nuclear cells by stimulation of the inferior olive shows that the actual conduction time is around 1 ms (5,17), which is expected for a monosynaptic pathway. However, even if the pathway is di- or even tri-synaptic this could not explain the extremely long latencies.

Another explanation could be that some excitatory input to the olive that is also activated by the stimulation, masks an early inhibition. Output from the cerebellar nuclei contacts mesencephalic structures collectively known as the mesodiencephalic junction (32,33). Some of these structures project to the inferior olive and make excitatory contact (32,34). This excitatory input is known to terminate in the same dendritic spine glomeruli as the inhibitory input from the cerebellar nuclei (35). However, lesions of the mesodiencephalic junction did not affect the NO inhibition or its latency (18).

Another possibility is that the long latency is due to slow receptor mechanisms. Slow hyperpolarizing responses have been known since the early 1980s (36). GABA_B receptors, which are present in the olive (37), have been shown to mediate IPSPs with onset latencies ranging from 18–50 ms in the hippocampus (38). There is also evidence that the α_3 subunit can slow activation of GABA_A receptors (39). The α_3 subunit is present in GABA_A receptors on the somata of olivary cells, which show delayed responses to GABA (40). These results are all from *in vitro* work and cannot automatically be applied to intact animals, but they encourage speculation that the long latency of NO inhibition is caused by receptor properties.

Functions of the NO pathway

The functions of the NO pathway are still an object of controversy and different views tend to reflect different views on the function of the climbing fibre system. When the inhibitory effects of the pathway were demonstrated, we suggested three different, though not necessarily mutually exclusive, functions: regulation of spontaneous Purkinje cell firing, regulation of learning and gating of sensory input to the olive (10).

Feedback regulation of spontaneous Purkinje cell activity

Purkinje cells have high spontaneous firing rates, usually around ~40–50 Hz. This spontaneous activity does not rely on excitatory input but is caused by intrinsic membrane properties of the Purkinje cell (41,42). Neurones in the cerebellar nuclei as well as neurones in the inferior olive are also spontaneously active (43,44).

Although the direct effect of climbing fibre input to the Purkinje cells is excitatory, the long-term effect is to depress spontaneous activity. An increase in olivary discharge rate over ~ 2 Hz will cause a strong suppression of simple spike firing (22,45,46). Conversely, if the Purkinje cell is deprived of climbing fibre input, there is a rapid (within seconds) increase in tonic firing (41,47,48).

The possible functions of this tonic climbing fibre effect have not been discussed very much in the literature. One speculation is that it can elicit prolonged responses or prolonged facilitation of defensive reflexes. Pain stimulation elicits a particularly strong excitation of the inferior olive, including prolonged high frequency firing (49). A persistent pain around the eye, for instance, would thus be expected to cause an increased climbing fibre input to Purkinje cells controlling the orbicularis oculi muscle that would disinhibit the nuclear cells and cause a prolonged blink or a prolonged facilitation of the blink reflex (50).

Whatever its function, the tonic effect of climbing fibre input on Purkinje cells is well established. We reasoned that an increased firing in the Purkinje cell would inhibit the nuclear neurones, disinhibit the olive and depress the Purkinje cells. The NO pathway would thus function as a negative feedback system for controlling the spontaneous simple spike firing of the Purkinje cells (10).

This hypothesis was recently tested by reversibly blocking and stimulating activity in the NO fibres while at the same time recording activity in single Purkinje cells (28). Blocking the NO pathway by injecting small amounts of lignocaine into the fibre bundle resulted in an increase in the rate of spontaneous olivary discharge from about 1 Hz to about 2 Hz and a strong suppression of Purkinje cell simple spike firing (Figure 3). Conversely, stimulation of the NO pathway resulted in a decreased olivary firing and an increased spontaneous activity in the Purkinje cells. These results demonstrate that the NO neurones, when firing at frequencies that are likely to occur naturally, can control spontaneous Purkinje cell firing. They strongly suggest that the NO pathway is part of a negative feedback system for controlling activity in the olivo-cerebello-olivary circuit. These results might explain the findings by Miall et al. (51) that simple spike firing predicts the occurrence of a complex spike in the Purkinje cell. It should perhaps also be emphasized here, that various ways of inactivating one part of the olivo-cerebellar circuit, while leaving the others intact, as has been attempted in many conditioning experiments, are unlikely to succeed. Inactivation of one part of the loop will clearly have profound effects on all the other parts.

It would seem that the effects of manipulating the NO pathway on Purkinje cells require that at least some of the NO effects are restricted to olivary cells

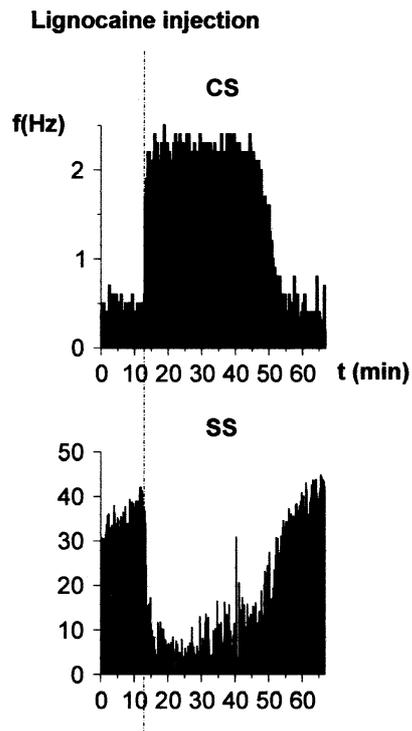


Figure 3. Purkinje cell activity after blockade of the nucleo-olivary pathway. Example histogram of complex spike (cs) and simple spike (ss) frequencies before and after a reversible blockade (lignocaine injection) of the nucleo-olivary pathway. Time of injection indicated in the figure. Bin width 10 s.

within the same microcomplex. If this were not the case, increased Purkinje cell activity in one cortical microzone would have disruptive feedback effects in other microzones where Purkinje cell activity was normal. This does not exclude the possibility that the NO fibres can project to olivary cells in other microcomplexes. As noted below, there are several different types of GABA receptors at different locations in the olivary neurones and some may be involved in different functions. It is conceivable that NO fibres terminate on one type of receptor in the same microcomplex and other receptor types in other microcomplexes.

Although we have chosen here to focus on the regulation of Purkinje cell activity, it should be remembered that it is activity in the entire olivary-cerebellar loop that is being regulated. Climbing fibres are known to contact several other types of neurones in the cortex as well as the nuclei (19,52,53) and may have regulatory effects on all of them. A consequence of the feedback system is that many cells in the olivo-cerebellar circuits are under constant influence from the cerebellar nuclei, the final output from the cerebellum. Furthermore, even if it is true that the system controls spontaneous activity of Purkinje cells, it also controls the nuclei and spontaneous activity of the inferior olive. Perhaps the critical aspect here is the balance between cerebellar and olivary activity.

Regulation of cerebellar learning

A second proposed function for the NO pathway is that it is part of a feedback system that controls associative cerebellar learning (10). This was based on the assumption that classical conditioning of a simple movement involves synaptic changes in the cerebellar cortex due to mossy fibre/parallel fibre activation by the conditioned stimulus and climbing fibre activation by the unconditioned stimulus (54,55). We reasoned that as neurones in the anterior interpositus nucleus learn to generate, say, a conditioned eyeblink, by increasing their firing in response to the conditioned stimulus, they will also provide an inhibitory signal to the inferior olive. As learning proceeds and nuclear output increases, the olive will gradually become more suppressed at the time of the unconditioned stimulus to the eye. Eventually, the climbing fibre signal to the cerebellum will be so weak that further learning ceases.

This hypothesis is supported by the observation that classically conditioned eyeblink responses were extinguished in decerebrate ferrets when the NO pathway was stimulated just before the eye stimulus in conditioning trials (56). Furthermore, it has been found that activity in the inferior olive is depressed during the expression of conditioned responses (Figure 4) (57,58). This depression correlates with the size of the conditioned response, is temporally specific and occurs specifically in the part of the rostral DAO that projects to blink related Purkinje cells (58). It also appears that classical conditioning does not occur until the NO pathway has developed (59).

NO inhibition may also explain the “blocking” phenomenon in classical conditioning. It was shown by Kamin (60) that, if learning has occurred to a particular conditioned stimulus, learning to a second conditioned stimulus, presented simultaneously, will be very inefficient. The first conditioned stimulus is said to “block” the second. A simple explanation for this is that the nuclear response elicited by the first conditioned stimulus causes an inhibition of the olive that prevents any association between the second conditioned stimulus and climbing fibre input from the eye (10). Direct evidence in support of this suggestion comes from an experiment in which injection of a GABA-blocker in the inferior olive prevented blocking (61).

A characteristic aspect of classical conditioning is the adaptive timing of the conditioned response. A conditioned blink response, for instance, is timed so that the maximum amplitude is reached at the time of the expected eye stimulus, when the protective effect is most valuable to the animal. Because of the long latency of NO inhibition, one would expect the conditioned response to be associated with an inhibition of the olive, only when the deep nuclear activity precedes the eye stimulus by 20–30 ms. This prediction was confirmed in experiments on decerebrate ferrets where we could compare the timing of conditioned responses and NO inhibition. Thus, although the mechanism is elusive, the long latency makes perfect physiological sense in this context. If NO inhibition were faster, a conditioned response that was too late to protect the eye, would still be able to suppress the olive and prevent further learning, clearly an undesirable feature of the

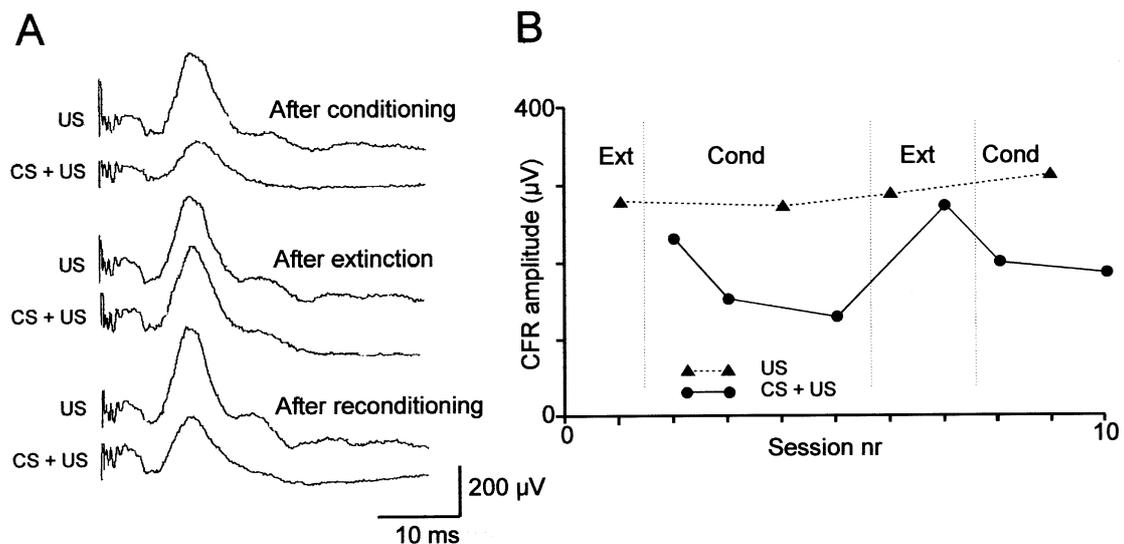


Figure 4. Inhibition of climbing fibre responses after conditioning and extinction. (A) Climbing fibre responses (averages of 10 trials) recorded in the c3 zone of the cerebellar cortex. The *upper trace* in each pair shows the control response evoked by the unconditioned stimulus (US) alone, and the *lower trace* the response to US when preceded by conditioned stimulus (CS). The *top pair* shows the depression of climbing fibre responses after about 600 trials of conditioning training (for details see ref. 58). The *middle pair* after 40 extinction trials and the *bottom pair* after 40 reconditioning trials. (B) Changes in the average amplitude of the climbing fibre responses over 20 consecutive trial sessions of conditioning (cond) and extinction (ext). Control sessions with only US presentation alternated with test sessions with both CS and US presentations. (Figure adapted from ref. 58.)

system. We have therefore argued that NO inhibition is actually a critical mechanism for regulating the appropriate timing of the conditioned response (18).

The crucial role of NO inhibition in conditioning is also highlighted by another recent study in which it was found that blocking NO inhibition can prevent extinction of a conditioned response (62). This finding suggests that for extinction to occur, it is not sufficient that the climbing fibre input elicited by the unconditioned stimulus is removed, but that climbing fibre input must actually be suppressed below the background level.

Gating of olivary input to the cerebellum

Recordings from Purkinje cells in walking cats have shown that olivary discharge elicited by tactile stimulation of the paws is suppressed if that stimulation is the result of purposeful movements by the animal (63). This gating of olivary transmission differs from the situation in eyeblink conditioning where the olivary input is not caused by the animal's own behaviour. Indeed, a conditioned blink may prevent input to the olive. Nevertheless, it has been suggested that the NO pathway also causes gating of olivary transmission during walking (10). If walking movements were generated by increased activity in the cerebellar nuclei, they would be expected to be accompanied by nuclear inhibition of the inferior olive. However, evidence from walking cats have not fully borne this out (64) although it is possible that NO inhibition is one of several mechanisms behind gating. For fuller discussions of the gating hypothesis, see refs 65 and 66).

Regulation of electrotonic coupling in the inferior olive

A very different proposal from the three discussed above is that the NO pathway regulates coupling between gap junctions between olivary neurones. The neurones of the inferior olive are known to make electrotonic dendro-dendritic connections (67–69). As GABA-ergic input to the olivary glomeruli has been reported to terminate close to gap junctions, it has been suggested that the NO pathway primarily controls electrotonic coupling between olivary cells (30,69).

It has been further proposed by Llinas and Welsh that the cerebellar nuclei, by controlling coupling of olivary cells, can determine the pattern of synchronized firing in corresponding groups of Purkinje cells, and that they are critically involved in coordination of different parts of the body in movement (70). Is it possible that the NO pathway could serve both as a feedback and a coordination function?

Llinas and Welsh argue that this is unlikely and that the evidence favours the coordination view. However, their theory raises a number of unresolved

questions. First, as noted above, NO fibres in a particular microcomplex seem to project to a relatively small group of olivary neurones within the same or adjacent microcomplexes and it is difficult to see how they could coordinate olivary cells belonging to microcomplexes controlling muscles in different parts of the body as would be required by the coordination theory. Second, the long latency of NO inhibition as well as the low conduction velocity of climbing fibres, make this system very slow and ill suited for the fast adjustments of movements characteristic of the cerebellum. Finally, mice in which the gene for connexin 36, an olivary gap junction protein, has been knocked out, have no obvious impairments in motor performance (71).

However, we think that there may be a way in which regulation of gap junctions could be reconciled with the role of climbing fibres in motor learning. If coupling of olivary neurones is confined to microcomplexes controlling synergistic movements, gap junctions could ensure spread of climbing fibre activity in a way that would amplify learned defensive reactions. In eyeblink conditioning, for instance, input from the cornea to olivary cells controlling blink could spread to cells controlling, say, head withdrawal. When a conditioned blink has been established, and head withdrawal therefore is less important, the NO pathway might turn off spread of excitation from the blink microcomplex, so that conditioned head withdrawal would extinguish.

Conclusion

The functions proposed for the NO pathway reflect different theories of the functions of the climbing fibre system. In our opinion, the view of the olivo-cerebellar system in which the climbing fibres, by signalling damage and movement errors, both regulate background activity of Purkinje cells and provide teaching signals to the cerebellum, is strongly supported by the evidence. The data reviewed above, which clearly support the suggestions that the NO pathway is involved in feedback control, fit very well with this general view of the cerebellum. However, there remain a number of important unresolved issues before we can fully understand the role of this projection. For instance, we know almost nothing about the effects of climbing fibres on nuclear cells and cortical interneurones. We also need answers to questions such as how specific is the NO projection and what are the characteristics of the receptors on which it terminates.

Acknowledgements

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