CLASSICAL HEART RATE CONDITIONING AND AFFECTIVE BEHAVIOR: THE ROLE OF THE CEREBELLAR VERMIS.

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INTRODUCTION

The correct functional interpretation of the cerebellum has taken more than two centuries during which consistent physiological and pathophysiological data have been accumulated to document beyond any doubt its involvement in skeletal motor regulation and coordination.

Hovever, besides its preminent role in somatic motor control, as early as 1856 (11) we have the first experimental evidence of the involvement of the cerebellum in the regulation of visceral reflex activities. Between 1937 and 1940 Moruzzi published some fundamental observations on the role of cerebellar vermis in the control of cardiovascular reflexes and described the inhibitory effect of vermal stimulation on the hypertension of baroreceptive origin (50, 51). These studies, besides assessing a precise role of the cerebellum in the coordination of the autonomic nervous system, suggested for the first time that the cerebellar effects on blood pressure and heart rate could be part of a more complex behavioral reaction. This hypothesis greatly influenced the subsequent investigations and opened the way to the findings by Zanchetti and Zoccolini (85) on the relationsip between the anterior vermis and the fastigial nucleus and the hypothalamically evoked visceral and behavioural manifestation of sham-rage in the decorticated cat. A few years earlier Snider (66) had already proposed an involvement of the cerebellum in affective and cognitive behaviour on the basis of its anatomical connections with the hypothalamus. This concept was reinforced in later years (see 78 for a review) when the possibility of a cerebellar modulation of the autonomic and limbic system was corroborated by further anatomical studies (69).

An important contribution which uncovered another non-motor role of the cerebellum came in the early twenties from the Soviet scientists of the Pavlov school, following the discovery of the conditioned reflexes (see 80 for a review). These and more recent studies concerning the effects of cerebellar lesion and electrical stimulation on different types of conditioned motor reflexes (13) have raised the important issue of a cerebellar contribution to learning and memory and some of the current models of conditioned reflexes like the eye blink response have been used as a test bench for the principal theories on cerebellar motor learning (4, 43). Along with conditioned somatic motor reflexes cerebellum appears to be involved in less specific conditioned responses of visceral origin such as condi-tioned bradycardia and some forms of aversive conditioned responses and behav-

iours. The cerebellar circuits involved and the different control mechanisms employed for the modulation of these categories of conditioned responses will represent the central issue of this review.

Very recently, reports of neuropsychological disorders in patients with cerebellar pathology documented by neuroimaging techniques (see 20 for a review), suggest a strong cerebellar involvement in the regulation of the speed, consistency and appropriateness of cognitive processes (63). This action may be topographically organized: the medial cerebellar regions being correlated with emotion and affection and the lateral parts with the control of thought, planning, memory , learning and language.

Thus, in spite of the methodological limitations imposed by the experiments on humans and the lack of unifying theoretical models to interpret the results obtained in studies ranging from conditioned reflex experiments to psychological tests, the hypothesis of a cerebellar involvement in non-motor, "high-order" processes, has taken form and, while is awaiting further confirmation, is continuously stimulating new experiments.

As already mentioned above, this review is focused on the influence of the cerebellar vermis on the acquisition, expression and development of unspecific conditioned responses, mainly of cardiovascular origin, and on the development of aversive behaviours to noxious stimuli and stressful situations.

I.   *Cerebellar vermis and responses to aversive stimuli.*

In general a reaction to an aversive situation represents a nonspecific combination of both autonomic (variation in heart rate and blood pressure, pupillary dilatation) and somatic (freezing, attack) responses. They are rather independent from the nature of the stimulus and indicate a modification of the psychological state of the animal which is related to an increased level of anxiety or fear. The hypothalamus and the limbic system represent the major nervous structures involved in their origin and both are anatomically linked with the cerebellum (66).

Indeed, Moruzzi (52) showed that in the acute hypothalamic cat, the electrical stimulation of the anterior vermis could abolish the sham-rage fits spontaneously occurring in this preparation. These observations were later developed by Zanchetti and Zoccolini (85) who could evoke a sham-rage fit in the thalamic cat by stimulating the rostral portion of the fastigial nucleus. Moreover, the disappearance of the response following decerebration, proved the hypothalamic involvement in the mediation of the cerebellar response. In line with these results is also the abolition of the pressor and depressor responses evoked by the hypothalamus obtained by the contemporary stimulation of the anterior cerebellar vermis (8).

More recently, Leaton and Supple (39) obtained evidence of the involvement of the cerebellar vermis in a series of complex behaviours elicited by aversive stimuli in the rat. The lesion of the vermis blocks the long-term habituation of the acoustic startle response, a typical aversive response produced by a sharp sound. The same authors reported an unusually lowered reactivity of the lesioned animals which

could be easily manipulated. A similar "taming" effect had been reported earlier by Berman *et al.* (10) and by Peters and Monijan (60) following a vermal lesion in the cat and in the monkey respectively, in the absence of detectable motor impairments. Although the mechanisms at the base of these "taming" effects are still unclear, they may possibly reflect a direct modulation by the cerebellum of complex affective behaviours (72). A decreased reactivity to fearful stimuli has been recently described in staggerer mutant mice (33, 46). These animals exhibit a 75% loss of Purkinje cells and an almost total loss of granule cells after the first postnatal month. The mutants are less fearful than normal mice and resemble mice with lateral amygdala lesions (47). These results may be explained by cerebellar influences on the limbic system (54, 69) and by the reciprocal hypotalamo-cerebellar connections (24). Cerebellar vermis seems to be involved also in the modulation of a series of specific behaviours which appear when the animal is confronted with fearful situations. In particular, vermal lesion decreases the "freezing" reaction induced in the rat by the sight of a predator. Similarly are reduced the "taste neophobia" and the enhancement of reactivity induced by chronic lesions in the ventromedial hypothalamus (71, 72). In accordance with the effects produced by lesion or genetic alteration of the cerebellar vermis, are the effects produced by electrical stimulation of the vermal cortex and of the cerebellar nuclei. These consist in a series of coordinated somatomotor and autonomic responses typical of a behavioural reaction to fearful situations. In the rat, somatomotor responses to stimulation of the medial cerebellum comprehend cringing, cowering and freezing behaviours and a potentiation of the acoustic startle response (3, 7, 12, 78). In the cat, rage and attack reactions have been described following stimulation of the cerebellar vermis (12,61,78,85). Electrical stimulation of the cerebellum during neurosurgery in man has been described to produce generalyzed sensations of anxiety and fear (53). Taken as a whole these results suggest a functional role of the cerebellar vermis in the modulation of a series of responses which may be different according to the animal species but they all reflect a central state of fear.

II.   *Cerebellar vermis and conditioned responses.*

According to Weinberger (79) classical Pavlovian conditioned responses (CRs) can be divided into two general categories: specific and nonspecific. Specific CRs are usually somatic motor responses (such as the extention of the nictitating membrane, the closure of the eyelid or the flexion of a limb) which are specific to the nature of the unconditioned stimulus and are interpreted as discrete defensive responses towards a potentially noxious stimulus. Nonspecific CRs include both autonomic (heart rate and blood pressure variations, pupillary dilatation, etc.) and diffuse somatic responses (behavioural stillness, freezing, etc.). They are independent from the nature of the unconditioned stimulus since they can be conditioned by different types of unconditioned stimuli of both aversive and appetitive nature. Nonspecific CRs are interpreted as a sign of a modified level of attention and are generally considered to be manifestations of conditioned arousal (58).

Since the first studies on cerebellar involvement in the control of CRs, it emerged a clear functional separation between medial and lateral cerebellum in the control of specific and nonspecific CRs. Electrophysiological and lesion studies indicate that classical eyelid or limb flexion conditioned responses are under the influence of the intermedio-lateral cerebellar cortex and interposed-dentate nuclei. The detailed analysis of this aspect of cerebellar involvement in associative learning processes is beyond the scope of this review (see: 13, 23, 33, 36, 81 for a comprehensive analysis). Here we shall briefly summarize the current hypotheses and the still unresolved issues.

1. - *Specific conditioned responses.*

Closure of the eyelid and extension of the nictitating membrane occurs in many species as a response to any potentially noxious stimulus applied to the cornea. This withdrawal reflex can be easily conditioned by pairing the noxious (unconditioned) stimulus with an innocuous (conditioned) acoustic stimulus. Several experimental evidence suggest the participation of the cerebellum in this form of motor learning. Selective lesions in area HVI of the cerebellar cortex or in the corresponding cerebellar nuclei (82, 83) impair or abolish the CR. Reflex blinks to the unconditioned stimulus and the acquisition of other concomitant autonomic CRs are not affected by the lesion (37). On the basis of anatomical findings, Thompson (77) has proposed a cerebellar memory circuit in which the somatosensory information about the unconditioned stimulus is relayed to the inferior olive and, via the climbing fibers, reaches the cerebellar cortex and nuclei where it converges with auditory informations concerning the conditioned stimulus projected via mossy fibers from the pontine nuclei. This circuit appears as a suitable working model for the Marr/Albus theory of cerebellar motor learning. Indeed, lesions in the inferior olive abolish nictitating membrane conditioning in the rabbit (44, 84). Furthermore, this CR can be obtained by substituting the acoustic conditioned stimulus with electrical stimulation of selected regions within the pontine nuclei (70).

However the view of the cerebellum as a storage site for motor memory traces has been challenged by reports on the possibility of nictitating membrane conditioning in decerebrate and decerebellate animals (30) and by the suspect that cerebellar lesions per se can induce performance deficits in the unconditioned eyeblink response (80). Thus the debate is still open on whether the essential and sufficient plasticity necessary for the classical conditioning of the eyeblink and other withdrawal reflexes resides exclusively in the cerebellum, or whether the memory traces are distributed among several parts of the neural circuits controlling the conditioned responses. Beyond this controversy, there is sufficient evidence to support the view that the lateral cerebellum plays an important role in the acquisition and in the performance of many types of learned motor behaviours.

2. - *Nonspecific conditioned responses.*

In a different perspective should be placed the role of the medial cerebellum in the modulation of nonspecific autonomic and behavioural conditioned responses.

We have seen in the preceeding section that the midline cerebellum, which includes the vermal cortex and the fastigial nucleus, is functionally involved in a variety of affective and fear-related behaviours. Moreover, its stimulation produces a series of variations in heart rate (2, 8, 17) blood pressure (19, 27, 48, 55), respiration (68) regional blood flow distribution (28, 40) baroreceptor reflex activity (51, 34). All these effects on autonomic variables have been evoked in acute, anaesthetized or decerebrate preparations. Recently, Bradley *et al.* (16) have shown that electrical stimulation at low intensity of the medial portion of lobule IX (uvula) in the conscious rabbit produces an increase in heart rate and blood pressure, a desynchronization of the EEG, pupillary dilatation and an increased activity in the EMG of neck and limb muscles accompanied by "pricking" of the ears. All the responses appear together at the same threshold current. This set of autonomic and somatic responses resembles very closely the manifestations typical of the alarm reaction, as described by Abrahams *et al.*(1), which represents a stereotyped reflex behaviour observed in every animal species when confronted with a sudden and unknown stimulus. Thus, the effects of electrical stimulation and lesion of the cerebellar vermis in both acute and chronic preparations, together with increasing neuroanatomical evidence on the connections existing between the cerebellum and several nervous structures controlling emotional behaviour like the ascending reticular formation (67), the limbic system and the hypothalamus (25, 26, 54, 70), the nucleus tractus solitarius and the periacqueductal gray (6, 9, 49) and the parabrachial nuclei (59) have prompted a series of investigations to examine the contribution of the vermis to the conditioned bradycardia, a classically conditioned fear-related autonomic response.

This vagus-mediated heart rate deceleration is one of the most representative among the nonspecific conditioned responses; it can be easily produced after a few conditioning trials in a variety of species (18, 21) including man (57), and can be evoked by different motivationally significant stimuli which may predict negative as well as positive reinforcement (32, 56). Originally considered as an index of associative learning, like the eyeblink and other specific conditioned responses, conditioned bradycardia is now believed to have a more general function. On the basis of results, obtained mainly in humans, which showed that bradycardia occurs during periods of attention, Lacey and Lacey (31, 32) have put forward the hypothesis that bradycardia is a component of an attentional or orienting mechanism aimed to enhance the receptivity and the response of the subject to sensory input. According to the hypothesis, bradycardia would enhance attention and information processing by decreasing the afferent activity in the arterial baroreceptors nerves. In fact baroreceptors input is known to produce EEG synchronization (an index of reduced arousal) and sleep (42), to increase the threshold of several reflex responses and to depress activity in sensory and motor neurons (32). This theory has been supported by several observations performed in experiments on humans. For example, while testing reaction times, a significant relationship has been found between visual acuity and the magnitude of the bradycardia developed following the presentation of an auditory attention commanding stimulus (62). Similarly,

Bohlin and Graham (14) have observed in humans that the development of a
bradycardic response following an anticipatory attention commanding cue was
always associated with an increase in amplitude and a decrease in the latency of
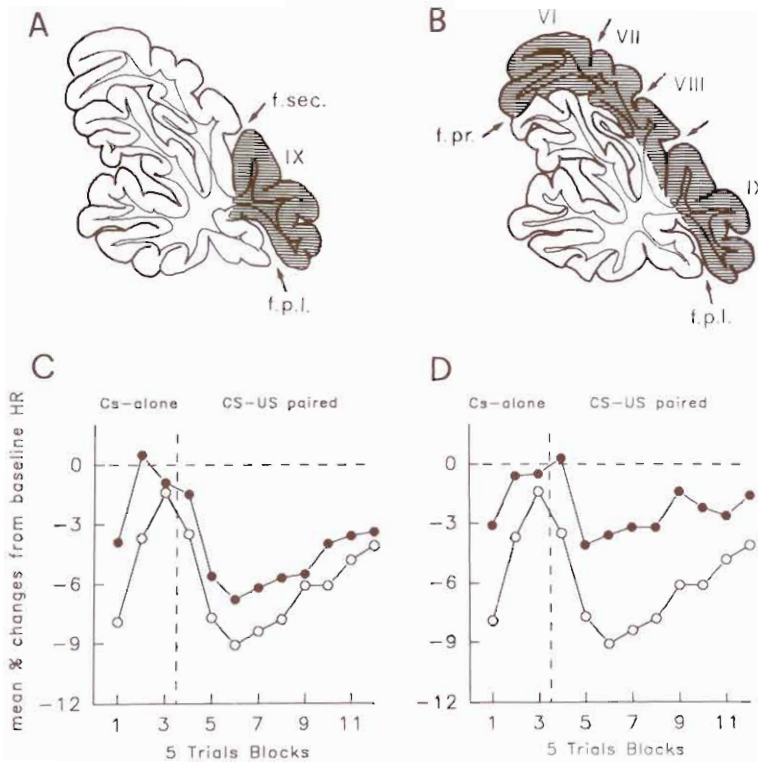the eyeblink response induced by an alerting stimulus.

Fig. 1 - *Effects of cerebellar posterior vermis lesions on the acquisition of fear-related heart rate
conditioned and unconditioned responses.*

A-B: the stippled area in the schematic drawings of representative sections through the cerebellum of
the rabbit, shows in the sagittal plane, the average extent of typical lobule IX (A) and posterior vermis
(B) lesions. Abbreviations: f.pr.= fissura prima; f.sec.= fissura secunda; f.p.l.= fissura posterolateralis.
C-D: mean percentage HR changes to the CS from pre-CS baseline during CS-alone and CS-US paired
presentations. The responses obtained in controls (open circles)are compared in C with those of lobule
IX lesioned animals (filled circles) and in D with those of posterior vermis lesioned animals (filled
circles). Data points represent means for five trial blocks.
Modified from Ref.64, Figs. 1 and 3.

At present there are rather few studies concerning the role of cerebellum in the
acquisition and expression of classically conditioned bradycardia. Removal of
most of the cerebellar vermis in the rat severely attenuates the acquisition of the
conditioned bradycardia without affecting unconditioned heart rate responses (75).

Furthermore, the effect is specific of the midline cerebellum since bilateral lesions of the cerebellar hemispheres, which deeply affect specific conditioned responses like the conditioned eyeblink, do not disrupt conditioned bradycardia (76). More recently, the essential role of the anterior vermis in the acquisition and retention of the conditioned bradycardia has been reassessed in the rabbit (74). Lesions of lobules III-VI, without damaging the fastigial nucleus, greatly reduce the acquisition of the conditioned bradycardia without disrupting baseline heart rate or unconditioned heart rate responses. Moreover, lesions of the vermis performed after the acquisition of conditioned bradycardia reduced evidence of prior conditioning, thus indicating a cerebellar effect also on the retention of the conditioned response. In the same laboratory the activity of the Purkinje cells in the anterior vermis of the rabbit has been recorded during differential bradycardia conditioning (73). The cellular responses to the two differential conditioned auditory stimuli occurred at rather short latencies (20-30 msec) and consisted either in an increased sustained activity or in a greater phasic discharge to the positive conditioned stimulus. These electrophysiological and lesion results clearly suggest that the anterior cerebellar vermis is part of a neural circuit important for the classically conditioned bradycardia.

In our laboratory, a series of experiments has been performed to investigate the role of the posterior vermis in conditioned bradicardia. The primary target of the experiments was lobule IX, due to its effects on cardiovascular and behavioural parameters observed in the acute and chronic rabbit following electrical and chemical stimulation (15, 16, 17). The results showed that selective lesion of lobule IX (Fig. 1A) did not affect the acquisition and the expression of conditioned bradycardia (Fig. 1C) thus indicating that the uvula does not play a primary role in the learning of the conditioned response, despite its well established cardiovascular control. On the contrary, the removal of the entire posterior vermis (Fig. 1B), always sparing the fastigial nucleus, produces a dramatic reduction in the amplitude of the conditioned bradycardia (Fig. 1D), without affecting the baseline heart rate or the unconditioned heart response (64). Moreover, in a group of rabbits lesioned after being submitted to the conditioning session, the bradycardic response developed when reconditioned was similar to their pre-lesion conditioned response (Fig. 2A, B). This indicates that the lesion of the posterior vermis does not impair the reacquisition of an already learned heart rate response and thus the posterior vermal cortex cannot be the locus of neuronal plasticity responsible for its learning and memory. These findings are similar to those reported for the habituation of the startle acoustic response in the rat (41) and are comparable to those obtained in the rabbit on reconditioning of the nictitating membrane response following lateral cerebellar cortex removal (38, 45). The conclusion that can be drawn by these results is that also the posterior vermis, particularly lobules VI-VII is important, although not essential, for the initial acquisition of the conditioned bradycardia, but it does not seem to be the site of its memory trace which may be situated in some extracortical structures such as the fastigial nucleus or even in some extracerebellar neural sites like the central nucleus of the amygdala whose lesion severely impairs the acquisition of the conditioned bradycardia in the rabbit (29).
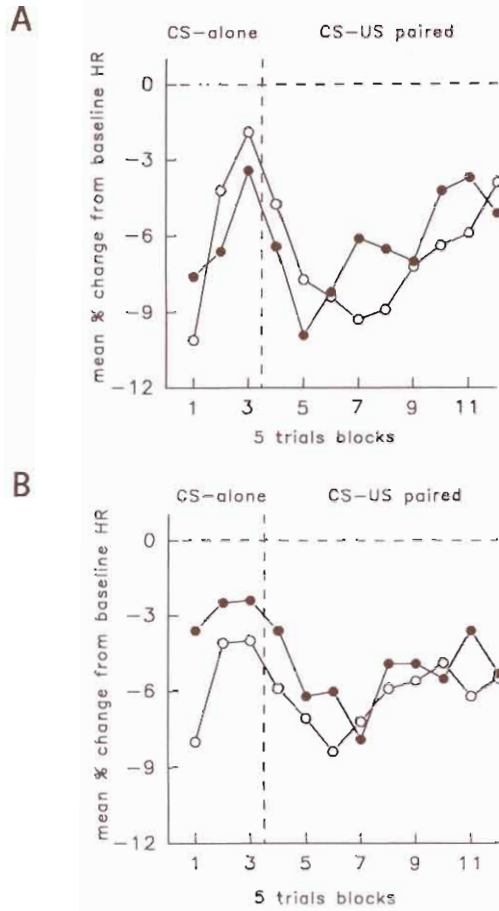
Fig. 2. - *Mean percentage HR changes to the CS from pre-CS baseline during CS-alone and CS-US paired presentations recorded during conditioning (open circles) and reconditioning (filled circles) sessions in the unoperated control group (A) and in the group submitted to posterior vermis lesion after the first conditioning (B).*

Data points represent means for five trial blocks.
Modified from Ref.64, Fig.6.

More recently we have investigated the development of the conditioned brady-cardia in neonatal rabbits (65). Surprizingly, this fear-related response appears in a form comparable to that of the adult rather late, around the 18th day of postnatal life, when the sensory and motor systems necessary for the conditioned association are already well developed and considerably later than other somatomotor condi-tioned responses (Fig. 3). This rather long period necessary for the maturation of the mechanisms mediating this conditioned response may be required by the complete functional development, among other nervous structures, of the cerebel-lar vermis which is undoubtly involved in the control of classically conditioned
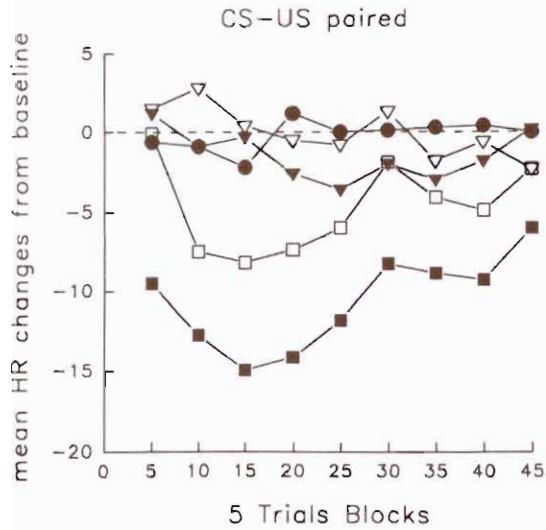
Fig. 3. - *Mean HR changes from pre-CS baseline recorded during CS-US paired presentations in rabbit of different postnatal ages.*

(Filled circles: 10 days; open triangles: 12 days; filled triangles: 15 days; open squares: 18 days; filled squares: adult). Data points represents means for five trials blocks.
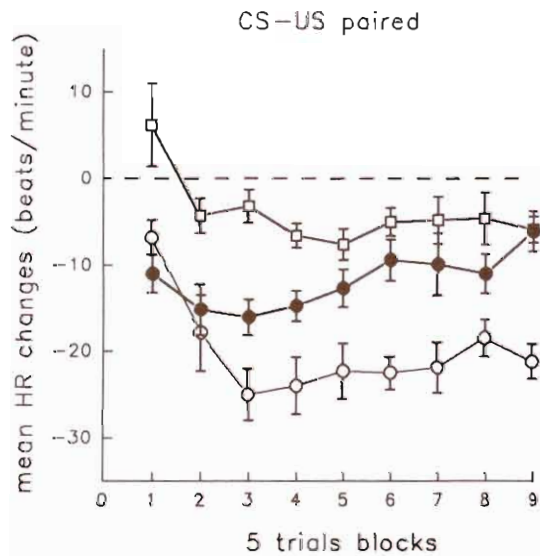Fom Ref.65, Fig.1.

Fig. 4. - *Mean HR changes from pre-CS baseline recorded during the CS-US paired presentations in controls (filled circles), animals submitted to cerebellar vermis ablation when 5-days-old (open circles) and animals submitted to cerebellar vermis ablation when 18-days old (open squares).*

Data points represent means for five trials blocks.

bradycardia in the adult and reaches its full maturation only some time after birth (5, 35). At present this hypothesis is being tested experimentally by submitting neonate rabbits to selective ablations of lobules V-VII of the cerebellar vermis at different periods before the 18th day of life and by comparing the conditioned bradycardia evoked when they have reached adulthood with that of intact animals. Preliminary results (22) indicate not only that lobules V-VII of the cerebellar vermis are essential for the correct development of the response but also that the timing of the lesion is a critical parameter which will permanently affect the characteristics of the bradycardic response in the adult (Fig. 4A-B). When the removal of lobules V-VII occurs around the 5th day of postnatal life, the magnitude of the conditioned bradycardia exibited by the adult rabbit is significantly larger than that of an intact control. On the contrary, if the removal of the same cerebellar lobules has taken place on the 18th day of life, when the conditioned bradycardia appears for the first time, the magnitude of the response tested in the adult is significantly smaller with respect to intact controls. At present, the mechanism responsible for this striking difference in the conditioned response following the same cerebellar lesion performed in different periods of postnatal development is not known and is being investigated.

CONCLUSIONS

The data reviewed above indicate that the cerebellum is involved in the control of affective behaviour and in the organization of classically conditioned somatic and autonomic responses. This influence follows a well defined anatomical and functional division of the organ: the lateral cerebellum, comprising the cortex of the hemispheres and the dentate and interposite nuclei, is concerned with the acquisition and expression of specific somatomotor conditioned responses such as the nictitating membrane response and some limb withdrawal reflexes. The midline cerebellum, comprising the vermal cortex and the fastigial nucleus, besides controlling specific forms of affective behaviour, influences the conditioning of non specific responses in which autonomic and somatic components are often present together. It is interesting to note that these responses, which are more or less linked to basic defensive necessities, are all under the control of the philogenetically older cerebellar vermis, where, starting from avians, specific circuits have developed which can modulate both autonomic and somatic reflexes in a coordinated, functionally meaningful reaction. Indeed, within the vermis there seems to be a well pronounced localization of functions. Anterior vermal cortex contains microzones which control somatic postural and reflex activity along with microzones which modulate cardiovascular and other autonomic reflexes. The posterior vermis, besides some areas controlling oculomotor reflexes and eye-head coordination, contains lobules, like the uvula, specifically involved in the control of autonomic responses and others, like lobules VI-VII, which modulate conditioned bradycardia. Moreover, these same lobules seem to play a role also in the development of the conditioned heart rate response during neonatal life.

Thus the cerebellar vermis can be considered as an important center for the coordination of several reflex activities under the control of the autonomic nervous system. However, as foreseen by Moruzzi, "these autonomic cerebellar effects may be part of a more complex behavioural reaction" and the separation of roles between medial and lateral cerebellum may leave place to a more unitary functional interpretation. In fact, if conditioned bradycardia, according to the hypothesis proposed by Lacey and Lacey (32), is a component of an attentional mechanism which enhances the speed and the performance of somatic reflex and volitional motor reactions, the control exerted by the cerebellar vermis on this response will contribute to the global motor coordination exerted by the rest of the cerebellum by dealing with the emotional and affective components which are always present in every goal-directed motor behaviour.

SUMMARY

The involvement of the cerebellar vermis in the control of affective behaviors and in the coordination of fear-related somatic and autonomic conditioned responses is reviewed in this paper.

In particular, the review focuses on the role of the midline cerebellum (vermis) on the acquisition and /or expression of classically conditioned bradycardia in the rabbit. The results of both lesioning and electrophysiological experiments indicate that the cortex of lobule III through VII is important, although not essential, in the acquisition and retention of this response, but it is not the site of its memory trace.

The time course of the development of the conditioned bradycardia in neonatal rabbits is also described. The results obtained are consistent with the possibility that the expression of conditioned bradycardia may depend on the complete maturation of cerebellum.

Moreover, preliminary data on the effects of the ablation of cerebellar vermis, performed at early stages of development, on the characteristics of conditioned bradycardia showed by adult rabbits are presented. These results indicate that cerebellar vermis is essential for the correct maturation of the response and that the timing of the lesion is critical for determining the characteristics of conditioned bradycardia in the adult.

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