Histol Histopath (1994) 9: 603-614

Histology and Histopathology

Invited Review

Hypothalamocerebellar and cerebellohypothalamic projections - circuits for regulating nonsomatic cerebellar activity?

E. Dietrichs[1,2], D.E. Haines[3], G.K. Røste[2,4] and L.S. Røste[1,2]

[1]Department of Neurology, The National Hospital, Oslo, Norway, [2]Department of Anatomy, Institute of Basic Medical Sciences, University of Oslo, Norway, [3]Department of Anatomy, University of Mississippi Medical School, Jackson, Mississippi, USA and [4]Department of Neurosurgery, The National Hospital, Oslo, Norway

Summary. Cerebellar involvement in visceral and affective responses is known from physiological and behavioral studies, but the pathways involved in these responses have remained enigmatic. Over the last ten years neuroanatomical studies have shown that the cerebellum and hypothalamus are interconnected by direct hypothalamocerebellar and cerebellohypothalamic projections and by a multitude of indirect pathways. The hypothalamocerebellar projection terminates in the cerebellar nuclei and in all layers of the cerebellar cortex as multilayered fibres. This projection is, at least in part, histaminergic. New immunocytochemical experiments indicate that small numbers of hypothalamocerebellar neurones may contain GABA- or glycine-like immunoreactivity. GABA may function as a transmitter in hypothalamocerebellar fibres, probably in conjunction with histamine, but it is not clear whether glycine may also function as a transmitter or only serve metabolic functions.

The bidirectional pathways between the cerebellum and hypothalamus may be part of the circuits through which the cerebellum participates in the modulation of a variety of nonsomatic events. In addition, new observations on patients with well localized cerebellar lesions reveal simultaneous somatic and visceral dysfunction. Recent research on direct hypothalamocerebellar pathways and on other connections between hypothalamus and cerebellum is reviewed. It is hypothesized that the cerebellum may act as a general modulator and coordinator of a wide range of central nervous activities, somatic as well as nonsomatic.

Key words: Cerebellum, Hypothalamus, Neuronal pathways, Multilayered fibres

Offprint requests to: Dr. Espen Dietrichs, M.D., Ph.D., Department of Neurology, The National Hospital, N-0027 Oslo, Norway

Introduction

It is well known that the cerebellum plays a regulatory role in somatic motor activities and equilibrium (see Brodal, 1981; Ito, 1984 for reviews). However, a growing body of data implicates that the cerebellum may also be involved in the control of nonsomatic activities. Thus, following cerebellar ablation or stimulation a multitude of visceral and affective responses has been reported, e.g., cardiovascular and endocrinological changes, altered respiration, intestinal motility and bladder tone, reduced aggressiveness, mood changes and alerting reactions (e.g., Moruzzi, 1940, 1950; Chambers, 1947; Dow and Moruzzi, 1958; Berman et al., 1974; Martner, 1975; Riklan et al., 1978; Del Bo, 1983a,b; Nakai et al., 1983; Nisimura and Kawaguchi, 1984; Nisimura and Watanabe, 1985; Chida et al., 1986; Williams et al., 1986; Bradley et al., 1987, 1990; Supple and Leaton, 1990). The consensus has been that such responses were mediated through brain stem reticular nuclei (Dow and Moruzzi, 1958; Ban, 1964; Martner, 1975), but some studies have shown that certain autonomic responses evoked by cerebellar stimulation may be abolished by precollicular decerebration or diencephalic coagulation (Zanchetti and Zoccolini, 1954; Sawyer et al., 1961). Similarly, Supple et al. (1988) found that behavioral responses induced by hypothalamic lesions could be modified by medial cerebellar lesions. The fibre connections involved in the cerebellar regulation of these nonsomatic responses have long remained an enigma. However, for the last ten years a series of investigations have revealed a complex network of direct and indirect pathways between hypothalamus and the cerebellum. It is reasonable to believe that these circuits may be directly involved in the modulation of nonsomatic activities. This report will summarize our current knowledge, briefly present some recent data

concerning these connections, and summarize observations from two patients whose lesions and subsequent clinical deficits bear directly on the topic at hand.

The hypothalamocerebellar projection

A direct pathway from the hypothalamus to the cerebellum was first demonstrated by retrograde transport of wheat germ agglutinin-horseradish peroxidase complex (WGA-HRP) in the cat (Dietrichs, 1984). Subsequent studies have revealed similar projections in rat (ter Horst and Luiten, 1986; Ericson et al., 1987; Dietrichs et al., 1992), tree shrew (Haines et al., 1985), bushbaby (Dietrichs and Haines, 1984), squirrel monkey (Haines and Dietrichs, 1984) and *Macaca* (Haines et al., 1990). Results from studies in turtle and clearnose skate may be taken to indicate the presence of hypothalamocerebellar fibres also in these species (Künzle, 1983; Smeets and Boord, 1985). The hypothalamocerebellar projection is bilateral with an ipsilateral preponderance (Fig. 1). It originates from various hypothalamic nuclei and areas, but mainly from the lateral, dorsal and posterior hypothalamic areas and the dorsomedial, ventromedial, supramammillary and tuberomammillary nuclei (Dietrichs and Zheng, 1984; Haines and Dietrichs, 1987).

It appears from the above mentioned studies that the number of hypothalamic neurones projecting to the cerebellum may increase as one ascends the phylogenetic scale from rat through tree shrew, prosimian primates and *Saimiri* to *Macaca*. In *Macaca* Haines et al. (1990) found about 1100 retrogradely labelled cells in the hypothalamus after an injection in the cerebellar nuclei. It is certainly reasonable to suggest that direct interconnections between the cerebellum and hypothalamus exist in humans and that such connections may be significant.

The trajectory of the hypothalamocerebellar fibres has been investigated by anterograde transport of various tracers (Dietrichs and Haines, 1985b; Dietrichs et al., 1985a; Haines et al., 1986; ter Horst and Luiten, 1986; Haines and Dietrichs, 1987). It appears from these studies that most of the descending axons course through the periaqueductal and periventricular grey (Fig. 1). They proceed from the periventricular grey around the

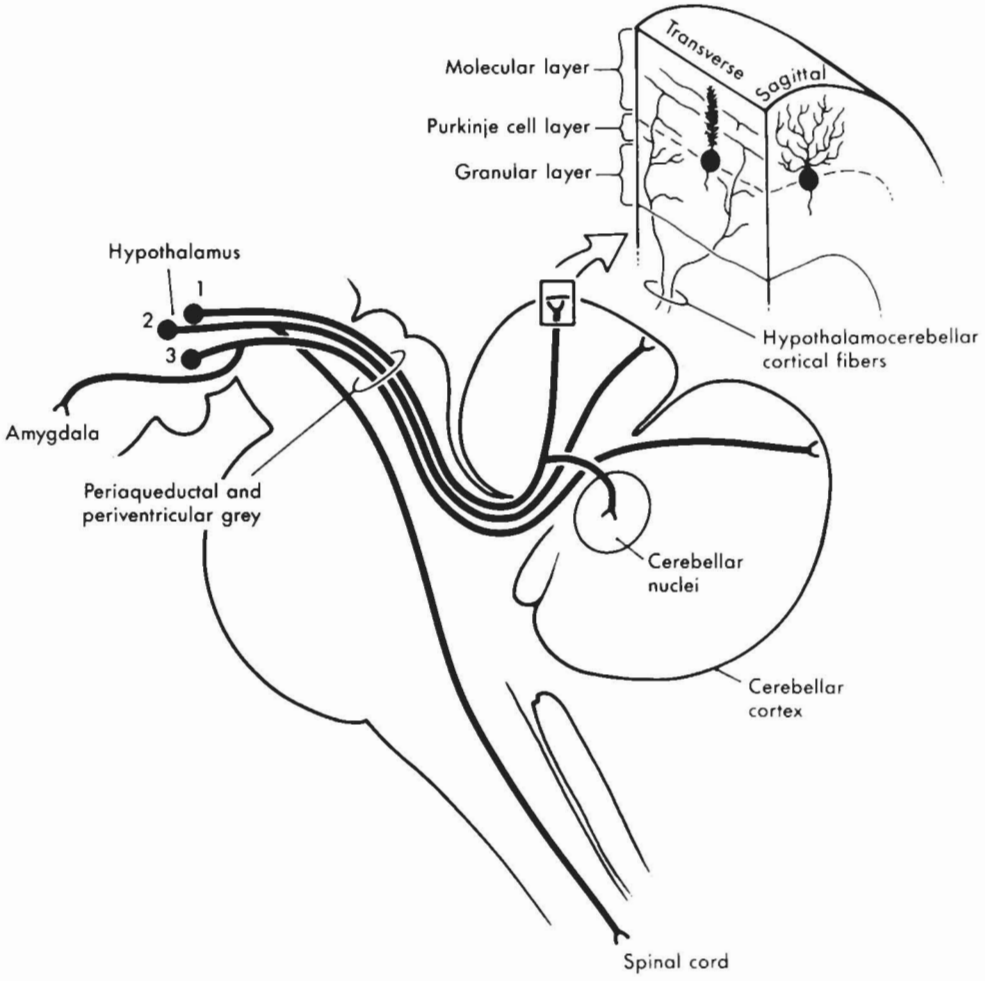

Fig. 1. Semidiagrammatic representation of the cerebellum, hypothalamus and brainstem in the sagittal plane showing the hypothalamocerebellar projections discussed in the text. Cell 1 shows a projection to the cerebellar cortex with collaterals to the cerebellar nuclei, cell 2 represents hypothalamic neurones whose axons collateralize to the cerebellum and spinal cord, and cell 3 is an example of hypothalamic neurones projecting to cerebellar structures and the amygdaloid complex. Hypothalamocerebellar projections are mainly uncrossed, although a minor component enters the contralateral cerebellum. Detail from the cerebellar cortex (upper right) shows how hypothalamocerebellar cortical fibres terminate in all layers of the cerebellar cortex as multilayered fibres.

medialmost part of the brachium conjuntivum and course into the cerebellar white matter. In addition, some fibres may enter the cerebellum from the reticular formation through brachium points (Haines et al., 1986).

Cerebellar cortical termination

The hypothalamocerebellar projection reaches all regions of the cerebellar cortex, but the main terminal areas appear to be the vermis and flocculus (Haines et al., 1986). We have shown that hypothalamocerebellar fibres terminate in all layers of the cerebellar cortex (Fig. 1-detail; Dietrichs and Haines, 1985b; Haines et al., 1986). Morphologically these fibres are neither mossy fibres nor climbing fibres, but have been classified as a third group of cerebellar cortical afferents, which we call *multilayered fibres* (Dietrichs and Haines, 1985b; Haines et al., 1986). Serotoninergic and noradrenergic afferents to the cerebellar cortex also terminate in this pattern (see, e.g., Hökfelt and Fuxe, 1969; Chu and Bloom, 1974; Chan-Palay, 1977; Takeuchi et al., 1982). Therefore, the term *multilayered fibres* is broadly applicable to *all* non-mossy and non-climbing fibre afferents to the cerebellar cortex. On their course from the folial white matter these fibres send branches to the granular and Purkinje cell layers (Fig. 1-detail). At various levels in the molecular layer these axons ramify, many travel parallel to the long axes of the folia (Fig. 1-detail). Although the ultrastructural features of these terminals have not yet been determined, it is certain that they form some type of functional synaptic contact.

Most likely all hypothalamocerebellar fibres terminate as multilayered fibres. However, a few mossy fibres were labelled in uvula and nodulus after large hypothalamic tracer injections in squirrel monkey (Haines et al., 1986). It is unclear whether these were true hypothalamocerebellar fibres or cerebellar afferents from nuclei bordering the hypothalamus (see Haines et al., 1986 for details).

Cerebellar nuclear termination

Hypothalamocerebellar fibres to the cerebellar nuclei (Fig. 1) have been demonstrated in studies using anterograde transport of WGA-HRP after injections in the hypothalamus (Dietrichs et al., 1985a) and retrograde transport of various tracers after injections and implantations in the cerebellar nuclei (Dietrichs and Haines, 1985a, Dietrichs et al., 1985a, 1994a; Haines et al., 1990). The cerebellar nuclear afferents originate within the same hypothalamic regions that project to the cerebellar cortex. In the cat, the hypothalamocerebellar nuclear projection reaches mainly the ipsilateral fastigial and interposed nuclei, but all cerebellar nuclei receive some afferents from the hypothalamus (Dietrichs et al., 1994a). Other experiments have given evidence for a strong projection to the interposed nuclei in *Macaca* (Haines et al., 1990).

Branching pattern of hypothalamocerebellar axons

The branching pattern of the hypothalamocerebellar projection has been addressed in retrograde fluorescent tracer studies (Fig. 1). Dietrichs and Zheng (1984) showed that some hypothalamic neurones project both to the cerebellar cortex and the spinal cord. In a triple labelling study Dietrichs and Haines (1986) found that other neurones project to the cerebellar cortex and amygdala.

A special point of interest has been whether hypothalamocerebellar cortical and nuclear fibres represent two different projections, or are solely branches of the same axons. In a recent study with depositions of one fluorescent tracer in the cerebellar nuclei and another in the overlying cerebellar cortex (Dietrichs et al., 1994a), we found that at least 50% of the hypothalamocerebellar nuclear fibres are branches from hypothalamocerebellar cortical axons (Fig. 1). However, due to methodological limitations this figure is undoubtedly low (Dietrichs et al., 1994a). It is probable that most, if not all, hypothalamocerebellar nuclear afferents are branches of axons bound for the cerebellar cortex. In addition to branches reaching the cerebellar cortex and nuclei, our experiments have revealed a further ramification so that many axons supply different parts of the cerebellar cortex, e.g., homologous lobules on the ipsilateral side and contralateral side.

Transmitters in hypothalamocerebellar fibres

Since some multilayered fibres contain noradrenaline or serotonin (see above), these would seem to be possible transmitter candidates in hypothalamocerebellar fibres. Indeed, since after lateral hypothalamic stimulation short latency responses in the cerebellar cortex were diminished under chlorpromazin treatment, Bratus and Yoltukhovsky (1986) concluded that the hypothalamocerebellar fibres were adrenergic. However, since the distribution of noradrenaline and serotonin containing neurones in the hypothalamus (see, e.g., Björklund and Nobin, 1973; Steinbusch, 1984) does not correspond to the origin of the cerebellar projection, these substances are probably not present in hypothalamocerebellar fibres. Instead, recent studies have given conclusive evidence that many multilayered fibres are histaminergic (Airaksinen and Panula, 1988; Inagaki et al., 1988; Airaksinen et al., 1989; Panula et al., 1989). Furthermore, it appears that these histaminergic fibres (e.g., Ericson et al., 1987; Airaksinen and Panula, 1988; Airaksinen et al., 1989) originate from those parts of the hypothalamus that contain the greatest concentration of retrogradely labelled cells subsequent to cerebellar injections of WGA-HRP (e.g., Dietrichs, 1984; Dietrichs and Haines, 1984; Haines and Dietrichs, 1984; Haines et al., 1990). Also, the results by Bratus and Yoltukhovsky (1986) would be in keeping with a histaminergic projection, since chlorpromazin is also

anti-histaminergic.

GABA and histamine appear to coexist in the same hypothalamic neurones (Takeda et al., 1984). Ottersen et al. (1987) have reported the presence of numerous glycine-like immunoreactive fibres in the baboon running horizontally in the transversal plane just superficial to the Purkinje cell layer, like multilayered fibres. The presence of glycine releasing terminals in the cerebellum has been suggested (Wiklund et al., 1982; Ottersen et al., 1988). Further studies of possible GABA or glycine (perphaps colocalized in histaminergic cells) in hypothalamocerebellar fibres have not been carried out. We have therefore recently performed some immunocytochemical experiments to find out whether GABA or glycine may also be found in hypothalamocerebellar neurones. These results are summarized below.

Immunocytochemical experiments

Four cats were used in experiments that combined retrograde tracing and immunocytochemistry. In each of these one of the following were injected into the cerebellar cortex and nuclei: 5 µl of 4% rhodamine-B-isothiocyanate (RITC), 7% Fast Blue, diluted rhodamine labelled latex microspheres or 2% WGA-HRP. The sections were incubated with GABA antiserum (GABA-25) diluted 1:200 in buffered 1% swine serum or glycine antiserum (Gly-31) diluted 1:100 in buffered 1% swine serum. The antisera, kindly provided by Dr. Jon Storm-Mathisen, were obtained from rabbits that had been immunized with glycine or GABA coupled to a carrier protein by means of glutaraldehyde (Storm-Mathisen et al., 1983; see also Ottersen et al., 1987, 1988). Specificity testing and processing were performed as described by Ottersen and Storm-Mathisen (1984).

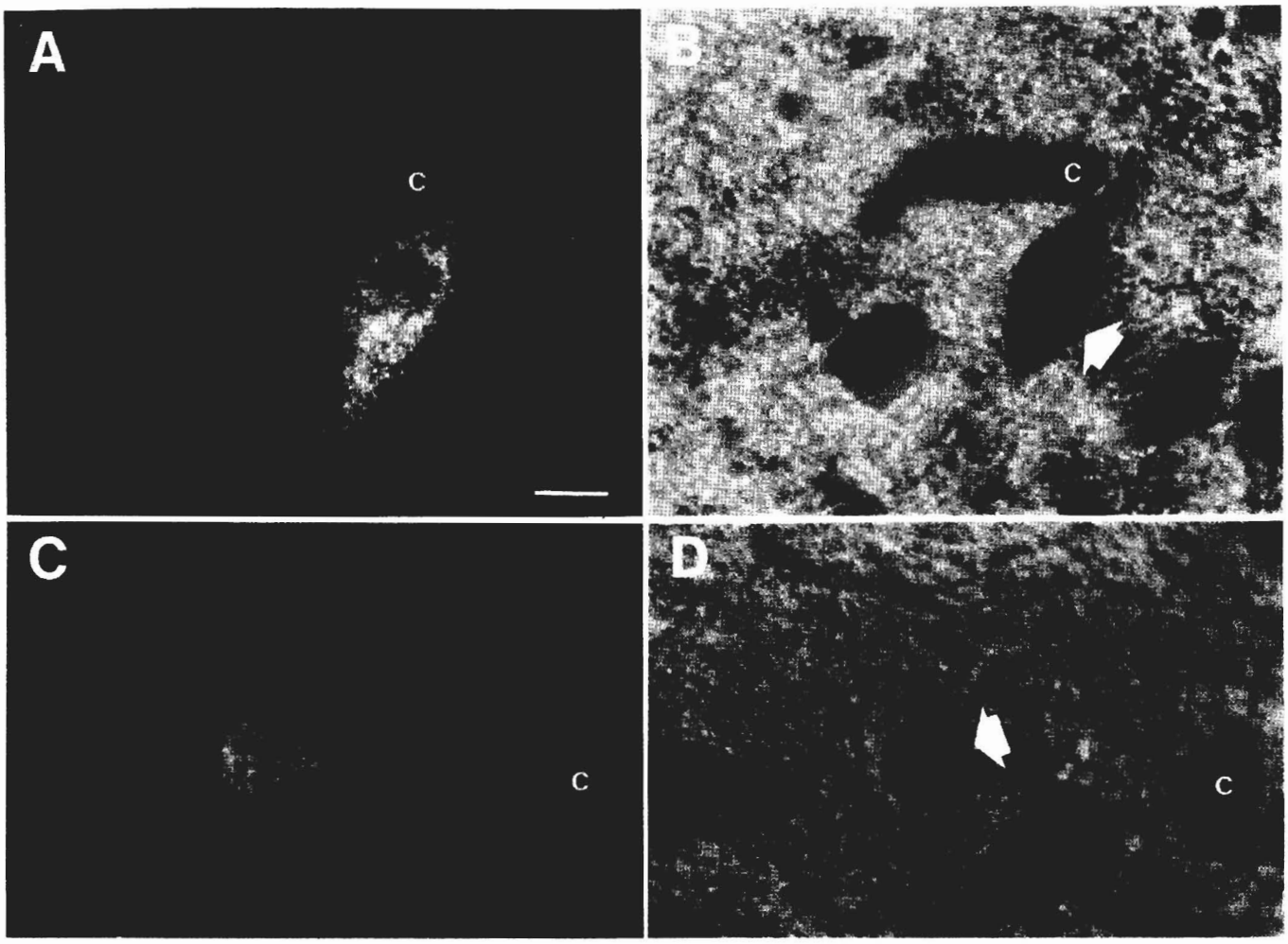

Fig. 2. Fluorescence photomicrographs from the lateral hypothalamic area in cat EPC 13 showing **(A,C)** neurones retrogradely labelled with RITC after cerebellar injection (exposed with 530 nm light). **B and D** show the same parts of the section exposed with 490 nm light for fluorescein to reveal GABA-like immunoreactivity. Note that one of the cells (arrow in B) shows no immunoreactivity, whereas the other cell (arrow in D) shows very faint staining. c: capillary. Bar= 15 µm; all same scale.

The three cases injected with fluorescent tracers all had a small number of retrogradely labelled hypothalamocerebellar neurones. In sections incubated with anti-GABA few cells in the posterior hypothalamus showed strong immunoreactivity, whereas neuropil labelling was dense in the entire region. Most of the retrogradely labelled neurones stood out as negative ghosts against the neuropil when examined for GABA-like immunoreactivity (Fig. 2A,B). However, four possible double labelled cells were found in the lateral hypothalamic area. A photomicrograph of one of these was shown by Dietrichs and Haines (1989; their Fig. 3). A few other cells showed very faint immunoreactivity of uncertain significance (Fig. 2C,D). Faint glycine-like immunoreactivity was found in many cells, but very few neurones showed strong immunoreactivity. None of the latter cells were double labelled, but many retrogradely labelled cells showed a weak glycine-like staining.

The cat injected with WGA-HRP had several hundred retrogradely labelled cells in the hypothalamus. Cells with GABA-like immunoreactivity were found scattered in the tuberomammillary and supramammillary nuclei and in the lateral, dorsal and posterior hypothalamic areas, and just inside the borders of the medial mammillary nucleus. Most of these cells showed only weak immunoreactivity, and only few cells were strongly labelled. None of the latter neurones were also labelled with WGA-HRP, whereas about 30 cells with weak GABA-like immunoreactivity were double labelled (Fig. 3A). These were located in the above mentioned nuclei and areas. Glycine-like immunoreactivity was found in most of the hypothalamic neurones, but the staining was faint in the vast majority of these. None of the cells with strongest glycine-like immunoreactivity were labelled with WGA-HRP, but a high number of weakly stained cells in various parts of the caudal hypothalamus were double labelled (Fig. 3B).

Different subpopulations?

These immunocytochemical results indicate that some hypothalamocerebellar neurones contain glycine-like immunoreactivity. However, since glycine may have metabolic functions, the occurrence in a neurone of glycine-like immunoreactivity can not be taken as conclusive evidence that glycine is a transmitter in this cell.

In our experiments few hypothalamocerebellar neurones showed GABA-like immunoreactivity. Clearly, the actual number of GABAergic neurones may be higher since there may be false negatives. The reported coexistence of histamine and GABA in hypothalamic neurones and the previous demonstrations of histaminergic hypothalamocerebellar neurones (see above), would lead to the assumption that some cerebellar projecting hypothalamic cells should contain GABA. On the other hand, it should also be stressed that the occurrence of GABA-like immunoreactivity in a neurone does not prove that GABA is the transmitter in this cell. Nonetheless, cerebellar projecting neurones seem to show a more widespread distribution within the hypothalamus than do the histaminergic neurons (see, e.g., Panula et al., 1984; Steinbusch and Mulder, 1984; Watanabe et al., 1984). This is taken to indicate that histamine and/or GABA may be transmitters in some, but *not all* hypothalamic fibres.

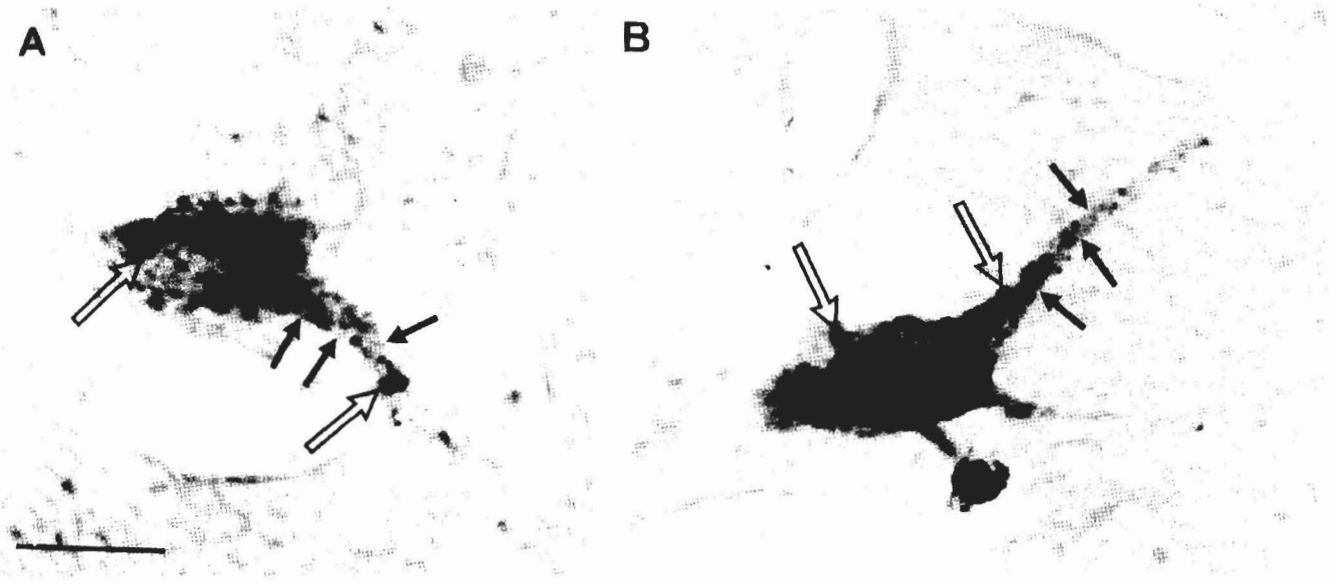

Fig. 3. Bright field photomicrographs from cat EPC 17. **A** shows a neurone in the region of the tuberomammillary nucleus double labelled by WGA-HRP retrogradely transported from the cerebellum (dark grains) and GABA-like immunoreactivity (arrowheads point to diffuse labelling of cytoplasm). Immunoreactive labelling of nerve terminals is out of focus. **B** shows a neurone in the lateral hypothalamic area double labelled by WGA-HRP (dark grains) and glycine-like immunoreactivity (arrowheads point to diffuse labelling of cytoplasm). Bar= 20 µm; both same scale.

When these data are taken into account, it seems probable that subpopulations of hypothalamocerebellar neurones with different transmitters may exist. One could also speculate whether some of these neurones used an excitatory amino acid transmitter. This has not yet been clarified, but Dietrichs et al. (1992) in a recent report failed to demonstrate a specific uptake mechanism for excitatory amino acids.

Due to their unique morphology, and since no other transmitters have been convincingly demonstrated, it is tempting to speculate that all multilayered fibres are monoaminergic. If so, histamine and possible dopamine would most likely be the transmitters.

Recent reports have given evidence that some multilayered fibres may contain dopamine (Wolters et al., 1988; Panagopoulos et al., 1991), enkephalin (King et al., 1987) or corticotropin-releasing factor (Cummings, 1989; Mugnaini and Nelson, 1989). It is still unclear which of these fibres may originate in the hypothalamus.

Indirect hypothalamocerebellar pathways

The existence of indirect neuronal connections from hypothalamus to the cerebellum has been proposed in physiological studies. After hypothalamic stimulation evoked potentials at various latencies have been recorded from the cerebellar cortex (e.g., Ban, 1964; Bratus and Yolthukovsky, 1986). However, the relay nuclei for such indirect pathways long remained unknown.

A series of different brain stem nuclei (Fig. 4) could act as potential relay stations for disynaptic and polysynaptic hypothalamocerebellar pathways. Thus, the hypothalamus gives origin to descending fibres, e.g., to the periaqueductal grey, the raphe nuclei, the dorsal motor vagal nucleus, the nucleus of the solitary tract, area postrema, the parabrachial nuclei and parts of the reticular formation proper (Veazey et al., 1982; Holstege, 1987). All these nuclei (Fig. 4) in turn project to the cerebellum (Chan-Palay, 1977; Pierce et al., 1977; Somana and Walberg, 1979a,b; Kotchabhakdi et al., 1980; Zheng et al., 1982; Dietrichs, 1983, 1988; Shapiro and Miselis, 1985).

In a recent study Ikai et al. (1992) found a dopaminergic projection to the cerebellar cortex from the ventral tegmental area. Since this region also receives afferents from the hypothalamus (Cruce, 1977), a hypothalamo-tegmento-cerebellar pathway should also be considered (see Fig. 4).

In addition to these connections, hypothalamic projections to some of the major precerebellar relay nuclei have now been demonstrated (Fig. 4). Both the inferior olive and the lateral reticular nucleus appear to receive sparse projections from the hypothalamus (Walberg, 1981; Dietrichs et al., 1985b), and a strong projection from the mammillary body to the pontine nuclei has been revealed (Aas and Brodal, 1988). The presence of a conspicuous hypothalamo-ponto-cerebellar pathway has been verified in experiments combining anterograde transport after hypothalamic tracer depositions with retrograde transport after cerebellar tracer depositions (Aas and Brodal, 1989). Quantitatively, this indirect pathway

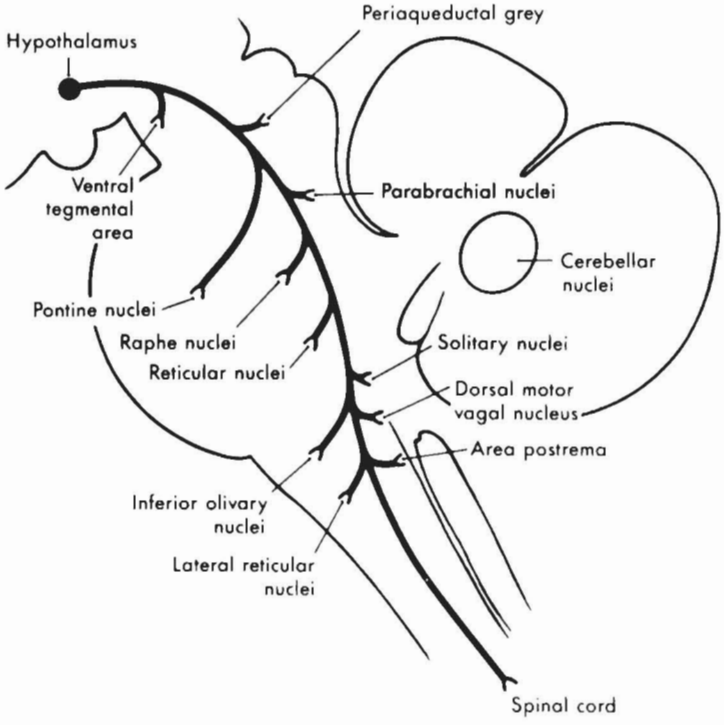

Fig. 4. Semidiagrammatic representation of the hypothalamus and brainstem showing the distribution of those descending hypothalamic fibres described in the text. Most, if not all, of those areas receiving hypothalamic input project to, among other targets, the cerebellar cortex and/or nuclei.

appears to be stronger than the direct connection. A topical arrangement has also been suggested. The hypothalamo-ponto-cerebellar fibres appear to have their main terminal area in lateral cerebellar regions, while the direct pathway primarily reaches the vermis. The posterior parts of the cerebellar hemispheres, especially the ventral paraflocculus, receive indirect input mainly from the medial mammillary nucleus, whereas the intermediate and lateral parts of the cerebellar anterior lobe receive such inputs from the dorsal, posterior and lateral hypothalamic areas (Aas and Brodal, 1988, 1989).

The cerebellohypothalamic projection

Sparse termination in the posterior hypothalamus after lesions in the cerebellum or brachium conjunctivum was described in some early reports (Wallenberg, 1905; Cohen et al., 1958; Jacobs, 1965; Martin et al., 1974). Furthermore, Whiteside and Snider (1953) after cerebellar stimulation recorded responses of short latency in the posterior hypothalamus. In spite of these observations, a possible cerebellohypothalamic projection was not mentioned in most previous studies.

Subsequent to the demonstration of direct hypothalamocerebellar fibres, we have also studied the distribution of cerebellohypothalamic fibres (Fig. 5) in cat (Dietrichs and Haines, 1985a), tree shrew (Haines et al., 1985), bushbaby (Dietrichs and Haines, 1984), squirrel monkey (Haines and Dietrichs, 1984; Haines et al., 1984) and *Macaca* (Haines et al., 1990). These investigations have revealed that all cerebellar nuclei give rise to a chiefly crossed projection to the posterior, dorsal and lateral hypothalamic areas and the dorsomedial nucleus (Fig. 5; see especially Haines et al., 1990).

The cerebellohypothalamic fibres appear to follow the route taken by cerebellothalamic fibres into the contralateral diencephalon, where they exit the main bundle and filter ventrally into the hypothalamus (Fig. 5). A relatively small proportion of these fibres appear to recross the midline (Fig. 5) to reach homologous parts of the ipsilateral hypothalamus (Dietrichs and Haines, 1985a; Haines et al., 1990). It remains for future studies to determine whether these direct cerebellohypothalamic fibres are a unique projection of their own, collaterals of cerebellothalamic axons, or a combination of these two patterns. The latter is the most likely situation (see Haines et al., 1985).

The cerebellohypothalamic projection shows a conspicuous contralateral preponderance, while the hypothalamocerebellar connection is mainly uncrossed. In spite of these patterns, there appears to be some degree of reciprocity. Thus, after depositions of WGA-HRP into the hypothalamus, some retrogradely labelled neurones in the cerebellar nuclei are surrounded by anterogradely labelled presumably terminal fibres (Dietrichs and Haines, 1985a; Dietrichs et al., 1985a), and similar observations are made in the hypothalamus after cerebellar nuclear tracer depositions (Dietrichs and Haines, 1984; Haines and Dietrichs, 1984; Haines et al., 1985, 1990).

Indirect cerebellohypothalamic pathways

In addition to short latency responses (see above), Whiteside and Snider (1953) also recorded medium and

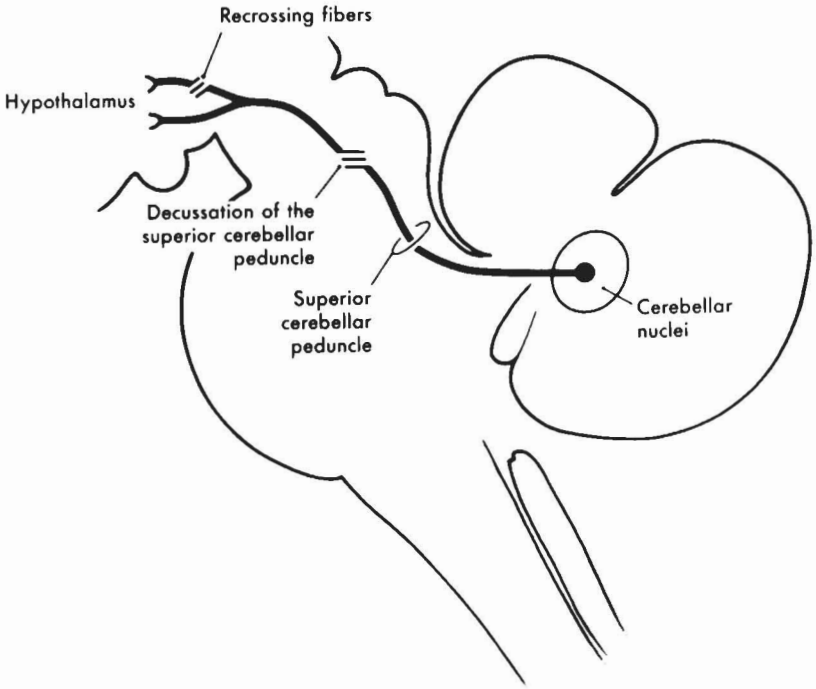

Fig. 5. Semidiagrammatic representation of the cerebellum and the hypothalamus in the sagittal plane showing the trajectory of cerebellohypothalamic axons as described in the text. These fibres cross in the decussation of the superior cerebellar peduncle. Although most appear to end contralateral to their origin, a few recross in the caudal hypothalamus to end ipsilaterally.

long latency responses from the hypothalamus after cerebellar stimulation. Thus, it is reasonable to assume that both disynaptic and multisynaptic hypothalamocerebellar pathways exist. Certain parts of the reticular formation proper are potential relay stations for disynaptic connections (see especially Del Bo and Rosina, 1986). In their double labelling study Del Bo and Rosina (1986) also found evidence for hypothalamocerebellar relays in the nucleus locus coeruleus and parabrachial nucleus. The presence of cerebellar efferents to the locus coeruleus complex has been disputed (see Dietrichs, 1988 for details), but species differences may exist. It appears that in some species axons from Purkinje cells in the posterior lobe vermis may reach these nuclei (Haines, 1975; Paton et al., 1991).

Functions of the hypothalamocerebellar circuits

Questions about the exact functions of the direct and indirect bidirectional pathways between the hypothalamus and cerebellum have remained unanswered, but several theories have been forwarded. First, it is well known that the cerebellum may be involved in the regulation of nonsomatic responses (see Introduction). Clearly, many such responses may be mediated directly through cerebellar influence on lower brain stem visceral centres, e.g., the paramedian reticular nucleus, nucleus parasolitarius, nucleus tractus solitarii and the parabrachial nuclei (Miura and Reis, 1969; Person et al., 1986; Paton and Spyer, 1992). However, since some of the autonomic responses seen after cerebellar manipulation are abolished by mesencephalic or diencephalic lesions (see Introduction), certain circuits involved in this aspect of cerebellar function must reach, at least, diencephalic levels. The cerebellum also appears to play a role in emotions such as fear, and the neuronal basis for this may be pathways to and from the reticular formation, the limbic system and the hypothalamus (Lalonde and Botez, 1990). It therefore seems reasonable to suggest that a system of interconnections between the cerebellum and hypothalamus represents a substrate through which the cerebellum may modulate/control a wide range of nonsomatic functions.

Another possibility is that the hypothalamocerebellar circuits only participate in motor control. Previous studies have shown that some parts of the hypothalamus, e.g., the lateral hypothalamic area, are involved in motor activities (Gladfelter and Brobeck, 1962; Wayner et al., 1981; Sinnamon et al., 1987). However, this possibility seems less likely because of the special morphological and chemical properties of the direct hypothalamocerebellar pathway.

Most likely, the direct and indirect connections between the cerebellum and various higher centres including the hypothalamus represent systems through which the cerebellum may receive and coordinate various types of information. It appears that the cerebellum may mediate a modality-specific modulation of sensory responses (Crispino and Bullock, 1984). Leiner et al. (1986, 1993) have further suggested that the cerebellum may contribute to mental skills. The cerebellum may not only play a role in learning of simple motor responses, but also be involved in learning of cognitive behaviours, spatial learning and discriminative learning (Lalonde and Botez, 1990). Aas and Brodal (1988, 1989) have suggested that the quantitatively important mammillo-ponto-cerebellar pathway may convey a motivational influence upon the initiation of, or learning of, movements, and that it may supply the cerebellum with information related to spatial memory and assist the planning and performance of spatially directed movements.

We have hypothesized that the cerebellum may be the primary brain centre responsible for integrating and coordinating information from various somatomotor, somatosensory, special sense and visceral systems to produce a coordinated response (Haines and Dietrichs, 1989). One example could be the visceral responses seen during locomotion. Clearly, these responses may be mediated via different systems, but the systems described here represent one alternative. The cerebellar nuclei may receive proprioceptive input through collaterals of spinocerebellar fibres or other cerebellar afferents. This information may be relayed to the hypothalamus and other visceral brain stem centres through direct and indirect pathways. They may, in a *feedforward* manner, prepare for an increased demand to the visceral motor system during somatic motor activity. Similarly, during sustained somatic motor activity the visceral responses could be continuously adjusted to demand in a *feedback* manner (Haines and Dietrichs, 1989).

Other phenomena, indicative of visceromotor interaction, may be mediated through hypothalamocerebellar and cerebellohypothalamic circuits. These include affectional and/or emotional influence on movement control and balance, or vice versa. One puzzling question, however, is why visceral dysfunction and emotional changes are *rarely* seen in patients with cerebellar lesions. Such a lack of symptoms could argue against a cerebellar role in nonsomatic control of viscerosomatic integration. Two factors come into play regarding this specific point. First, the brain exhibits a remarkable degree of compensation (plasticity?) subsequent to chronic cerebellar lesions. Even though different manifestations of ataxia dominate the clinical picture after cerebellar damage, conspicuous affective responses have been reported after cerebellar surgery and electrical stimulation in humans (see Riklan et al., 1978; van Buren et al., 1978). Second, many lesions in the cerebellum produce general increases in intracranial pressure or result in direct pressure on the pons and/or medulla oblongata. Although these patients may exhibit some visceral deficits, it is impossible to determine if the visceral dysfunctions are related to the cerebellar lesion or to affection of brainstem visceral centres.

Preliminary clinical observations

We have recently seen two patients (one in Oslo, one in Jackson) with well localized (on MRI) vascular lesions in the cerebellum (Dietrichs et al., 1994b; Haines et al., 1994). In both patients there was no evidence of other CNS pathology and no evidence of increased intracranial pressure or displacement of cerebellar or brainstem structures. The first patient (male, 60 years old) had a small hematoma about 1 cm in diameter in the left fastigial nucleus and adjacent white matter. He exhibited severe gait ataxia, bradycardia and hypoventilation. While his gait improved and his respiration returned to normal, the bradycardia persisted. The second patient (male, 73 years old) also had a left side cerebellar hematoma which involved parts of the anterior lobe cortex, rostral parts of the dentate, emboliform and probably fastigial nucleus, and adjacent parts of the brachium conjunctivum. He exhibited profound intention tremor in the left arm and leg. *Concurrent with the intention tremor* this patient had a pronounced flushing over his face and complained of feeling very hot. This visceral motor response/perception did not appear before or after the intention tremor, but *only during* the abnormal somatic motor movements. Those disrupted cerebellar circuits that account for the somatic tremor *simultaneously* produced abnormal visceral motor responses (Haines et al., 1994). Interestingly enough, this second patient *also* exhibited an obvious affective response (pathological laughter) that also appeared concurrent with the somatic and visceral signs (Doorenbos et al., 1993).

In both these patients a *single lesion* produced simultaneous somatic and visceral motor dysfunction. These observations support the hypothesis (see Haines and Dietrichs, 1989) that the cerebellum actively regulates visceral functions via the direct and indirect interconnections between the hypothalamus and cerebellum as described above. Furthermore, this takes place simultaneously with the cerebellar regulation of somatic motor activity.

Concluding remarks

Together with the results from numerous experimental studies (see Introduction), our own and other clinical observations indicate that the cerebellum is involved not only in motor control, but also in the regulation of various visceral and affective responses. The finding that the direct hypothalamocerebellar pathway is at least partly histaminergic (see especially Airaksinen et al., 1989; Dietrichs et al., 1992), and that it, like other monaminergic afferents, terminate as multilayered fibres (Dietrichs and Haines, 1985b; Haines et al., 1986), may be taken to support the notion that this connection has a broader regulatory role. The histaminergic system have been reported to regulate various activities, such as arousal state, brain energy metabolism, locomotor activity, neuroendocrine, autonomic and vestibular functions, drinking, sexual behavior and analgesia (Wada et al., 1991). Pollard and Schwartz (1987) have suggested that histaminergic neurones do not transmit discrete sensorimotor information, but instead modulate the sensitivity of target neurones to more discrete inputs. Together with the other direct and indirect bidirectional pathways between the cerebellum and various nonsomatic centres, the circuits between hypothalamus and the cerebellum thus may be part of a system enabling the cerebellum to act as a general modulator and coordinator of a wide variety of central nervous activities, somatic as well as nonsomatic.

Ackwnowledgements. The authors express their sincere appreciation to Drs. McDonald, Doorenbos and Haerer, Department of Neurology, The University of Mississippi Medical Center for access to the Jackson patient, to Dr. Jon Storm-Mathisen, Department of Anatomy, University of Oslo for providing antiserum against glycine and GABA, to Ms. A.T. Bore for expert technical assistance, to Ms. Myriam Kirkmann for her excellent renderings of Figures 1, 4 and 5, to Ms. Gail Rainer for typing, and to Mr. Gunnar F. Lothe and Mr. William deVeer for photography.

References

Aas J.-E. and Brodal P. (1988). Demonstration of topographically organized projections from the hypothalamus to the pontine nuclei: an experimental anatomical study in the cat. J. Comp. Neurol. 268, 313-328.

Aas J.-E. and Brodal P. (1989). Demonstration of a mammillo-ponto-cerebellar pathway. A multi-tracer study in the cat. Eur. J. Neurosci. 1, 61-74.

Airaksinen M.S. and Panula P. (1988). The histaminergic system in the guinea pig central nervous system: An immunocytochemical mapping study using an antiserum against histamine. J. Comp. Neurol. 273, 163-186.

Airaksinen M.S., Flügge G., Fuchs E. and Panula P. (1989). Histaminergic system in the tree shrew brain. J. Comp. Neurol. 286, 289-310.

Ban T. (1964). The hypothalamus, especially on its fiber connections, and the septo-preoptico-hypothalamic system. Med. J. Osaka Univ. 15, 1-83.

Berman A.J., Berman D. and Prescott J.W. (1974). The effect of cerebellar lesions on emotional behaviour in the rhesus monkey. In: The cerebellum, epilepsy, and behaviour. Cooper I.S., Riklan M. and Snider R.S. (eds). Plenum Press. New York. pp 277-284.

Björklund A. and Nobin A. (1973). Fluorescence histochemical and microspectrofluorometric mapping of dopamine and noradrenaline cell groups in the rat diencephalon. Brain Res. 51, 193-205.

Bradley D.J., Gherlarducci B., Paton J.F.R. and Spyer K.M. (1987). The cardiovascular responses elicited from the posterior cerebellar cortex in the anaesthetized and decerebrate rabbit. J. Physiol. 383, 537-550.

Bradley D.J., Gherlarducci B., La Noce A. and Spyer K.M. (1990). Autonomic and somatic responses evoked by stimulation of the cerebellar uvula in the conscious rabbit. Exp. Physiol. 75, 179-186.

Bratus N.V. and Yoltukhovsky M.V. (1986). Electrophysiological analysis of hypothalamic influences on the cerebellar cortex. Fiziol. Zh.

SSSR 32, 257-263.

Brodal A. (1981). Neurological anatomy in relation to clinical medicine. 3rd ed. Oxford University Press. New York. Oxford.

Chambers W.W. (1947). Electrical stimulation of the interior of the cerebellum in the cat. Am. J. Anat. 80, 55-93.

Chan-Palay V. (1977). Cerebellar dentate nucleus: Organization, cytology and transmitters. Springer. Berlin.

Chida K., Iadecola C., Underwood M.D. and Reis D.J. (1986). A novel vasodepressor response elicited from the rat cerebellar fastigial nucleus: The fastigial depressor response. Brain Res. 370, 378-382.

Chu N.-S. and Bloom F.E. (1974). The catecholamine-containing neurons in the cat dorsolateral pontine tegmentum: Distribution of the cell bodies and some axonal projections. Brain Res. 66, 1-21.

Cohen D., Chambers W.W. and Sprague J.M. (1958). Experimental study of the efferent projections from the cerebellar nuclei to the brainstem of the cat. J. Comp. Neurol. 109, 233-259.

Crispino L. and Bullock T.H. (1984). Cerebellum mediates modalityspesific modulation of sensory responses of midbrain and forebrain in rat. Proc. Natl. Acad. Sci. USA 81, 2917-2920.

Cruce J.A.F. (1977). An autoradiographic study of the descending connections of the mammillary nuclei of the rat. J. Comp. Neurol. 176, 631-644.

Cummings S.L. (1989). Distribution of corticotropin-releasing factor in the cerebellum and precerebellar nuclei of the cat. J. Comp. Neurol. 289, 657-675.

Del Bo A. and Rosina A. (1986). Potential disynaptic pathways connecting the fastigial pressor area and the paraventricular nucleus of the hypothalamus in the rat. Neurosci. Lett. 71, 37-42.

Del Bo A., Sved A.F. and Reis D.J. (1983a). Fastigial stimulation releases vasopressin in amounts that elevate arterial pressure. Am. J. Physiol. 244, H687-H694.

Del Bo A., Ross C.A., Pardal J.F., Saavedra J.M. and Reis D.J. (1983b). Fastigial stimulation in rats releases adrenomedullary catecholamines. Am. J. Physiol. 244, R801-R809.

Dietrichs E. (1983). Cerebellar cortical afferents from the periaqueductal grey in the cat. Neurosci. Lett. 41, 21-26.

Dietrichs E. (1984). Cerebellar autonomic function: Direct hypothalamocerebellar pathway. Science 223, 591-593.

Dietrichs E. (1988). Cerebellar cortical and nuclear afferents from the feline locus coeruleus complex. Neuroscience 27, 77-91.

Dietrichs E. and Haines D.E. (1984). Demonstration of hypothalamocerebellar and cerebello-hypothalamic fibres in a prosimian primate *(Galago crassicaudatus)*. Anat. Embryol. 170, 313-318.

Dietrichs E. and Haines D.E. (1985a). Observations on the cerebellohypothalamic projection, with comments on non-somatic cerebellar circuits. Arch. Ital. Biol. 123, 133-139.

Dietrichs E. and Haines D.E. (1985b). Do hypothalamocerebellar fibres terminate in all layers of the cerebellar cortex? Anat. Embryol. 173, 279-284.

Dietrichs D.E. and Haines D.E. (1986). Do the same hypothalamic neurons project to both amygdala and cerebellum? Brain Res. 364, 241-248.

Dietrichs E. and Haines D.E. (1989). Interconnections between hypothalamus and cerebellum. Anat. Embryol. 179, 207-220.

Dietrichs E. and Zheng Z.-H. (1984). Are hypothalamo-cerebellar fibres collaterals from the hypothalamo-spinal projection? Brain Res. 296, 225-231.

Dietrichs E., Walberg F. and Haines D.E. (1985a). Cerebellar nuclear afferents from feline hypothalamus demonstrated by retrograde transport after implantation of crystalline wheat germ agglutinin-horseradish peroxidase complex. Neurosci. Lett. 54, 129-133.

Dietrichs E., Haines D.E. and Qvist H. (1985b). Indirect hypothalamocerebellar pathway? Demonstration of hypothalamic efferents to the lateral reticular nucleus. Exp. Brain Res. 60, 483-491.

Dietrichs E., Wiklund L. and Haines D.E. (1992). The hypothalamocerebellar projection in the rat: Origin and transmitter. Arch. Ital. Biol. 130, 203-211.

Dietrichs E., Røste G.K., Røste L.S., Qvist H.L. and Haines D.E. (1994a). The hypothalamocerebellar projection in the cat - branching and nuclear termination. Arch. Ital. Biol. 132, 25-38.

Dietrichs E., Haines D.E., McDonald E.F., Doorenbos D.I. and Haerer A. (1994b). Visceral manifestations of cerebellar disease: Anatomical basis and clinical observations. Acta Neurol. Scand. (in press).

Doorenbos D.I., Haerer A.F., Payment M. and Clifton E.R. (1993). Stimulus-specific pathologic laugther: A case report with discrete unilateral localization. Neurology 43, 229-230.

Dow R.S. and Moruzzi G. (1958). The physiology and pathology of the cerebellum. University of Minnesota Press. Minneapolis. pp 50-396.

Ericson H., Watanabe T. and Köhler C. (1987). A morphological analysis of the tuberomammillary nucleus in the rat brain. Delineation of subgroups using antibody against L-histidine decarboxylase as a marker. J. Comp. Neurol. 263, 1-24.

Gladfelter W.E. and Brobeck J.R. (1962). Decreased spontaneous locomotor activity in the rat induced by hypothalamic lesions. Am. J. Physiol. 203, 811-817.

Haines D.E. (1975). Cerebellar corticovestibular fibers of the posterior lobe in a prosimian primate, the lesser bushbaby *(Galago senegalensis)*. J. Comp. Neurol. 160, 363-398.

Haines D.E. and Dietrichs E. (1984). An HRP study of hypothalamocerebellar and cerebello-hypothalamic connections in squirrel monkey *(Saimiri sciureus)*. J. Comp. Neurol. 229, 559-575.

Haines D.E. and Dietrichs E. (1987). On the organization of interconnections between the cerebellum and hypothalamus. In: New concepts in cerebellar neurobiology. King J.S. (ed). Alan R. Liss. New York. pp 113-149.

Haines D.E. and Dietrichs E. (1989). Non-somatic cerebellar circuits: A broader view of cerebellar involvement in locomotion. J. Motor Behav. 21, 518-525.

Haines D.E., Dietrichs E. and Sowa T.E. (1984). Hypothalamocerebellar and cerebello-hypothalamic pathways: A review and hypothesis concerning cerebellar circuits which may influence autonomic centers and affective behaviour. Brain Behav. Evol. 24, 198-220.

Haines D.E., Sowa T.E. and Dietrichs E. (1985). Connections between the cerebellum and hypothalamus in tree shrew *(Tupaia glis)*. Brain Res. 328, 367-373.

Haines D.E., Dietrichs E., Culberson J.L. and Sowa T.E. (1986). The organization of hypothalamocerebellar cortical fibres in the squirrel monkey *(Saimiri sciureus)*. J. Comp. Neurol. 250, 377-388.

Haines D.E., May P.J. and Dietrichs E. (1990). Neuronal connections between the cerebellar nuclei and hypothalamus in *Macaca fascicularis*: Cerebello-visceral circuits. J. Comp. Neurol. 299, 106-122.

Haines D.E., Dietrichs E., McDonald E.F., Doorenbos D.I. and Haerer A. (1994). Evidence of cerebellar influence on visceral motor function: A report on two patients. Anat Rec. (in press).

Hökfelt T. and Fuxe K. (1969). Cerebellar monoamine nerve terminals, a new type of afferents fibers to cortex cerebelli. Exp. Brain Res. 9,

63-72.

Holstege G. (1987). Some anatomical observations on the projections from the hypothalamus to brainstem and spinal cord: an HRP and autoradiographic tracing study in the cat. J. Comp. Neurol. 260, 98-126.

Ikai Y., Takada M., Shinonaga Y. and Mizuno N. (1992). Dopaminergic and non-dopaminergic neurons in the ventral tegmental area of the rat project, respectively, to the cerebellar cortex and deep cerebellar nuclei. Neuroscience 51, 719-728.

Inagaki N., Yamatodani A., Ando-Yamamoto M., Tohyama M., Watanabe T. and Wada H. (1988). Organization of histaminergic fibers in the rat brain. J. Comp. Neurol. 273, 283-300.

Ito M. (1984). The cerebellum and neural control. Raven Press. New York.

Jacobs V. (1965). The cerebellofugal system in the tarsius *(Tarsiidae carbonarius)* and the marmoset *(Oedipomidas oedipus)*. Dissertation. University of Kansas.

King J.S., Ho R.H. and Bishop G.A. (1987). The origin and distribution of enkephalin-like immunoreactivity in the opossum's cerebellum. In: New concepts in cerebellar neurobiology. King J.S. (ed). Alan R. Liss. New York. pp 1-28.

Kotchabhakdi N., Hoddevik G.H. and Walberg F. (1980). The reticulo-cerebellar projection in the cat as studied with retrograde transport of horseradish peroxidase. Anat. Embryol. 160, 341-359.

Künzle H. (1983). Supraspinal cell populations projecting to the cerebellar cortex in the turtle *(Pseudemys scripta elegans)*. Exp. Brain Res. 49, 1-12.

Lalonde R. and Botez M.I. (1990). The cerebellum and learning processes in animals. Brain Res. Rev. 15, 325-332.

Leiner H.C., Leiner A.L. and Dow R.S. (1986). Does the cerebellum contribute to mental skills? Behav. Neurosci. 100, 443-454.

Leiner H.C., Leiner A.L. and Dow R.S. (1993). Cognitive and language functions of the human cerebellum. TINS 16, 444-447.

Martin G.F., King J.S. and Dom R. (1974). The projections of the deep cerebellar nuclei of the opossum, *Diedelphis marsupialis virginiana*. J. Hirnforsch. 15, 545-573.

Martner J. (1975). Cerebellar influences on autonomic mechanisms. An experimental study in the cat with special reference to the fastigial nucleus. Acta Physiol. Scand. (Suppl) 425, 1-42.

Miura M. and Reis D.J. (1969). Cerebellum: a pressor response elicited from the fastigial nucleus and its efferent pathway in the brainstem. Brain Res. 13, 595-599.

Moruzzi G. (1940). Paleocerebellar inhibition of vasomotor and respiratory carotid sinus reflexes. J. Neurophysiol. 3, 20-31.

Moruzzi G. (1950). Problems in cebellar physiology. C.C. Thomas. Springfield Ill.

Mugnainini E. and Nelson B.J. (1989). Corticotropin-releasing factor (CRF) in the olivo-cerebellar system and the feline olivary hypertrophy. In: The olivocerebellar system in motor control. Strata P. (ed). Exp. Brain Res., Series 17. Springer. Berlin Heidelberg. pp 187-197.

Nakai M., Iadecola C., Ruggiero D.A., Tucker L.W. and Reis D.J. (1983). Electrical stimulation of cerebellar fastigial nucleus increases cerebral cortical blood flow without change in local metabolism: evidence for an intrinsic system in brain for primary vasodilation. Brain Res. 260, 35-49.

Nisimura U. and Kawaguchi Y. (1984). Excitatory effects on renal sympathetic nerve activity induced by stimulation at two distinctive sites in the fastigial nucleus of rabbits. Brain Res. 304, 372-376.

Nisimura U. and Watanabe Y. (1985). A depressant area in the lateral nodulus-uvula of the cerebellum for renal sympathetic nerve activity and systemic blood pressure in the rabbit. Neurosci. Res. 3, 177-181.

Ottersen O.P. and Storm-Mathisen J. (1984). Glutamate- and GABA-containing neurons in the mouse and rat brain, as demonstrated with a new immunocytochemical technique. J. Comp. Neurol. 229, 374-392.

Ottersen O.P., Davanger S. and Storm-Mathisen J. (1987). Glycine-like immunoreactivity in the cerebellum of rat and Senegalese baboon, *Papio papio*: A comparison with the distribution of GABA-like immunoreactivity and with (^{3}H)glycine and (^{3}H)GABA uptake. Exp. Brain Res. 66, 211-221.

Ottersen O.P., Stom-Mathisen J. and Somogyi P. (1988). Colocalization of glycine-like and GABA-like immunoreactivities in Golgi cell terminals in the rat cerebellum: A postembedding light and electron microscopic study. Brain Res. 450, 342-353.

Panagopoulos N.T., Papadopoulos G.C. and Matsokis N.A. (1991). Dopaminergic innervation and binding in the rat cerebellum. Neurosci. Lett. 130, 208-212.

Panula P., Yang H.-T. and Costa E. (1984). Histamine containing neurons in the rat hypothalamus. Proc. Natl. Acad. Sci. (USA) 81, 2572-2576.

Panula P., Pirvola S., Auvine S. and Airaksinen M.S. (1989). Histamine-immunoreactive nerve fibers and terminals in the rat brain. Neuroscience 28, 585-610.

Paton J.F. and Spyer K.M. (1992). Brain stem regions mediating the cardiovascular responses elicited from the posterior cerebellar cortex in the rabbit. J. Physiol. 427, 533-552.

Paton J.F., La Noce A., Sykes R.M., Sebastiani L., Bagnoli P., Gherlarducci B. and Bradley D.J. (1991). Efferent connections of lobule IX of the posterior cerebellar cortex in the rabbit - some functional considerations. J. Auton. Nerv. Syst. 36, 209-224.

Person R.J., Dormer K.J., Bedford T.G., Andrezik J.A. and Foreman R.D. (1986). Fastigial nucleus modulation of medullary parasolitary neurons. Neuroscience 19, 1293-1301.

Pierce E.T., Hoddevik G.H. and Walberg F. (1977). The cerebellar projection from the raphe nuclei in the cat as studied with the method of retrograde transport of horseradish peroxidase. Anat. Embryol. 152, 73-87.

Pollard H. and Schwartz J.C. (1977). Histamine neuronal pathways and their functions. TINS 10, 86-89.

Riklan M., Halgin L., Shulman M., Cullinan T. and Cooper I.S. (1978). Behaviour alterations following acute, shorter-term, and longer-term cerebellar stimulation in human. In: Cerebellar stimulation in man. Cooper I.S. (ed). Raven Press. New York. pp 161-183.

Sawyer C.H., Hillard J. and Ban T. (1961). Autonomic and EEG responses to cerebellar stimulation in rabbits. Am. J. Physiol. 200, 405-412.

Shapiro R.E. and Miselis R.R. (1985). The central neural connections of the area postrema of the rat. J. Comp. Neurol. 234, 344-364.

Sinnamon H.M., Ginzburg R.N. and Kurose G.A. (1987). Midbrain stimulation in the anesthetized rat: Direct locomotor effects and modulation of locomotion produced by hypothalamic stimulation. Neuroscience 20, 695-707.

Smeets W.J.A.J. and Boord R.L. (1985). Connections of the lobus inferior hypothalami of the clearnose skate *Raja eglanteria*. J. Comp. Neurol. 234, 380-392.

Somana R. and Walberg F. (1979a). The cerebellar projection from the

parabranchial nucleus in the cat. Brain res. 172, 144-149.

Somana R. and Walberg F. (1979b). Cerebellar afferents from the nucleus of the solitary tract. Neurosci. Lett. 11, 41-47.

Steinbusch H.W.M. (1984). Serotonin-immunoreactive neurons and their projections in the CNS. In: Handbook of chemical neuroanatomy. Vol. 3. Classical transmitters and transmitter receptors in the CNS, part II. Björklund A., Hökfelt T. and Kuhar M.J. (eds). Elsevier Science Publishers B.V. pp 68-125.

Steinbusch H.W.M. and Mulder A.H. (1984). Immunohistochemical localization of histamine in neurons and mast cells in rat brain. In: Handbook of chemical neuroanatomy. Vol. 3. Classical transmitters and transmitter receptors in the CNS, part II. Björklund A., Hökfelt T. and Kuhar M.J. (eds). Elsevier Science Publishers B.V. pp 126-140.

Storm-Mathisen J., Leknes A.K., Bore A.T., Vaaland J.L., Edminson P., Haug F.-M.S. and Ottersen O.P. (1983). First visualization of glutamate and GABA in neurones by immunocytochemistry. Nature 301, 517-519.

Supple W.F.Jr. and Leaton R.N. (1990). Lesions of the cerebellar vermis and cerebellar hemispheres: effects on heart rate conditioning in rats. Behav. Neurosci. 14, 934-947.

Supple W.F.Jr., Cranney J. and Leaton R.N. (1988). Effects of lesions of the cerebellar vermis on VMH-lesion-induced hyperdefensiveness, spontaneous mouse killing, and freezing in rats. Physiol. Behav. 42, 145-153.

Takeda N., Inagaki S., Shiosaka S., Taguchi Y., Oertel W., Tohyama M., Watanabe T. and Wada H. (1984). Immunohistochemical evidence for the coexistence of histidine decarboxylase-like and glutamate decarboxylase-like immunoreactivities in nerve cells in the magnocellular nucleus of the posterior hypothalamus of rats. Proc. Natl. Acad. Sci. USA 81, 7647-7650.

Takeuchi Y., Kimura H. and Sano Y. (1982). Immunohistochemical demonstration of serotonin-containing nerve fibers in the cerebellum. Cell Tissue Res. 226, 1-12.

Ter Horst G.J. and Luiten P.G.M. (1986). The projections of the dorsomedial hypothalamic nucleus in the rat. Brain Res. Bull. 16, 231-248.

van Buren J.M., Wood J.H., Oakley J. and Hambrecht F. (1978). Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. J. Neurosurg. 48, 407-416.

Veazey R.B., Amaral D.G. and Cowan W.M. (1982). The morphology and connections of the posterior hypothalamus in the cynomolgus monkey *(Macaca fascicularis)*. II. Efferent connections. J. Comp. Neurol. 297, 135-156.

Wada H., Inagaki N., Yamatodani A. and Watanabe T. (1991). Is the histaminergic neuron system a regulatory center for whole-brain activity? TINS 14, 415-418.

Walberg F. (1981). The diencephalo-olivary projection in the cat as studied with retrograde transport of horseradish peroxidase. Anat. Embryol. 163, 223-234.

Wallenberg A. (1905). Sekundäre Bahen aus dem frontalen sensiblen Trigeminuskerne des Kaninchens. Anat. Anz. 26, 145-155.

Watanabe T., Taguchi Y., Shiosaka S., Tanaka J., Kubota H., Terano Y., Tohyama M. and Wada H. (1984). Distribution of the histaminergic neuron system in the central nervous system of rats; a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. Brain Res. 295, 13-25.

Wayner M.H., Barone F.C. and Loullis C.C. (1981). The lateral hypothalamus and adjunctive behavior. In: Handbook of the hypothalamus. Vol 3. Part B, Behavioral studies of the hypothalamus. Morgane P.S. and Panksepp J. (eds). Marcel Dekker Inc. New York. pp 107-145.

Whiteside J.A. and Snider R.S. (1953). Relation of cerebellum to upper brain stem. J. Neurophysiol. 16, 397-413.

Wiklund L., Toggenburger G. and Cuénod M. (1982). Aspartate: possible neurotransmitter in cerebellar climbing fibers. Science 216, 78-80.

Williams J.L., Robinson P.J. and Lutherer L.O. (1986). Inhibitory effects of cerebellar lesions on respiration in the spontaneously breathing, anesthetized cat. Brain Res. 399, 224-231.

Wolters J.G., De Vente J. and Steinbush H.W.M. (1988). An atlas of the dopaminergic system in the rat brain, based on immunohistochemistry using antibodies to dopamine. Eur. J. Neurosci. (Suppl). 287.

Zanchetti A. and Zoccolini A. (1954). Autonomic hypothalamic outbursts elicited by cerebellar stimulation. J. Neurophysiol. 17, 475-483.

Zheng Z.-H., Dietrichs E. and Walberg F. (1982). Cerebellar afferent fibres from the dorsal motor vagal nucleus in the cat. Neurosci. Lett. 32, 113-118.