Cardiovascular Modules in the Cerebellum

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Abstract: Mapping with local lesions, electrical or chemical stimulation, or recording evoked field potentials or unit spikes revealed localized representations of cardiovascular functions in the cerebellum. In this review, which is based on literatures in the field (including our own publications), I propose that the cerebellum contains five distinct modules (cerebellar corticonuclear microcomplexes) dedicated to cardiovascular control. First, a discrete rostral portion of the fastigial nucleus and the overlying medial portion of the anterior vermis (lobules I, II and III) conjointly form a module that controls the baroreflex. Second, anterior vermis also forms a microcomplex with the parabrachial nucleus. Third, a discrete caudal portion of the fastigial nucleus and the overlying medial portion of the posterior vermis (lobules VII and VIII) form another module controlling the vestibulosympathetic reflex. Fourth, the medial portion of the uvula may form a module with the nucleus tractus solitarius and parabrachial nucleus. Fifth, the lateral edge of the nodulus and the uvula, together with the parabrachial nucleus and vestibular nuclei, forms a cardiovascular microcomplex that controls the magnitude and/or timing of sympathetic nerve responses and stability of the mean arterial blood pressure during changes of head position and body posture. The lateral nodulus-uvula appears to be an integrative cardiovascular control center involving both the baroreflex and the vestibulosympathetic reflex. [The Japanese Journal of Physiology 54: 431–448, 2004]

Key words: cardiovascular, cerebellum, fastigial, vermis, nodulus.

I. Introduction

In the 17th century, Thomas Willis attempted to localize the site of the central control of the viscera in the cerebellum [1]. Therefore, the involvement of the cerebellum in autonomic nervous system functions is a three-century-old idea. Nevertheless, this had been forgotten or only superficially mentioned until about 60 years ago when cerebellar electrical stimulation effects on various autonomic nervous system functions, such as vasomotor reflex [2], blood pressure wave and carotid sinus reflex [3], somatic and autonomic manifestations of sham rage [4] and contraction of pupils and nictitating membranes [5] were discovered. Reports on the effects of cerebellar electrical stimulation on arterial blood pressure, heart rate and respiration followed, but these early findings must be evaluated with caution because the possible spread of stimulating currents to outside the cerebellum was not accurately controlled at that time.

During the past four to five decades, research on the cerebellum has advanced markedly and our knowledge about its functional involvements and neuronal mechanisms has been conspicuously improved [6–10]. A new concept regarding the cerebellum has thus developed. The cerebellum has a unique modular structure, including a cortical microzone, a small group of nuclear neurons and a small group of inferior olive neurons, which are mutually interconnected to form a cerebellar corticonuclear microcomplex (hereafter, abbreviated as microcomplex). Each microcomplex contains a uniform neuronal circuit that is capable of learning based on activity-dependent synaptic plasticity. And each one is attached to an
extracerebellar system of diverse nature, endowing it with a unique adaptive mechanism.

This article summarizes current knowledge about the cardiovascular control functions of the cerebellum with reference to its module concept. I will first introduce some background knowledge regarding cardiovascular control and the cerebellum (sections II–IV), and then proceed to the main theme on the cerebellar control of cardiovascular functions (sections V–VII). During the past three decades, I have devoted my work to defining the involvement of the small lateral region extending through the dorsal nodulus and encroaching the ventral uvula of the cerebellum (hereafter abbreviated as the lateral nodulus-uvula) in cardiovascular control. The specification of this particular module will be made in some detail in section VIII.

II. Central Control of the Cardiovascular System

As summarized by Jodan [11], cardiovascular control, especially of the blood vessels, is mediated mainly by the sympathetic nervous system. The author therefore adopted the recording of renal sympathetic nerve activity (RSNA) as representing neural command signals for cardiovascular control (see Figs. 4, 5, 7, and 10) together with measurements of blood pressure and heart rate, which represent the final outputs of cardiovascular control.

Figure 1 illustrates possible structures involved in cardiovascular control. Preganglionic sympathetic neurons are within the intermediolateral cell column (IML) in the lateral horn of the spinal cord [12]. This region of the IML is projected from brainstem structures, such as A5, caudal raphe nuclei, the rostral ventrolateral medulla (RVLM) and the dorsomedial region of the nucleus tractus solitarius (NTS) in the medulla, Kölliker-Fuse nucleus (KFN) in the pons and some neurons in the paraventricular nucleus (PVN) in the hypothalamus [13]. There is evidence that one group of presympathetic neurons in the RVLM is of especially important in cardiovascular control [14]. Since arterial blood pressure falls markedly when pentobarbiton or an inhibitory amino acid, glycine, is applied to a restricted region of the ventral medulla surface, neurons in the RVLM may exhibit tonic basal firing. Furthermore, it was proposed that the tonic activity of the defense area in the hypothalamus provides the basis of tonic activity of RVLM neurons because the chemical or electrical lesioning of the RVLM abolishes the cardiovascular responses to

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Fig. 1. Central control of cardiovascular functions. A: Central nervous system structures involved in cardiovascular control. B: Coronal section of rat brain showing anatomical location of some of these structures. For abbreviations see text.
the stimulation of the hypothalamic defense area [15]. On the other hand, some vasomotor RVLM neurons exhibit an intrinsic pacemaker activity [14]. Resting discharges in these neurons are modified by inputs from various sources; arterial baroreceptor inputs decrease their activity, whereas inputs from chemoreceptors, from the hypothalamic defense area, and from the periaqueductal gray matter increase it. Parabrachial nucleus (PBN) and vestibular nuclei (VN) are also involved in cardiovascular functions.

These brainstem structures perform individual cardiovascular control functions, such as baroreflex, chemoreflex, and vestibulospinal reflex under regulatory influences from other regions. The stimulation of the central nucleus of the amygdala, the anterior hypothalamus, or the cerebellum, leads to changes in heart rate, blood pressure, respiration, and hind-limb vascular resistance [1, 11, 16]. Apparently these “other” regions modulate or integrate individual reflex responses to correspond to various environmental conditions. The purpose of this article is to review the efforts of locating cerebellar modules specifically dedicated to cardiovascular functions and to identify their regulatory influences on the brainstem cardiovascular centers.

### III. Functional Localization in the Cerebellum

The mammalian cerebellum can be divided along the longitudinal (anterior-posterior) and transverse (right-left) axes (Fig. 2). Longitudinally, the cerebellum consists of a central structure, the vermis, and two wings, the hemispheres. An intermediate part is distinguished from the lateral part of a hemisphere. The vermis is further subdivided into longitudinal zones A and B, the intermediate part into C1, C2, and C3 zones, and the hemisphere into D1 and D2 zones [17, 18]. Transversely, the fissura posterolateralis (f.p.l.) divides the cerebellum into the flocculonodular lobe (vestibular cerebellum) and the corpus cerebelli; the fissura prima (f. pr.) subdivides the corpus cerebelli into the anterior and posterior lobes. Shallow fissures subdivide the anterior and posterior lobes into a series of lobules, which are given specific names [19]. Larsell [20] introduced another nomenclature system in which he identified 10 lobules (I-X) in the vermis and corresponding HI-HX lobules in the two hemispheres. Some lobules are further subdivided into sublobules (a, b, c, d, and e) as shown in Fig. 2 [21]. The cerebellar nuclei are named the fastigial (F),

![Fig. 2. Localization of cardiovascular areas in rabbit cerebellum. A: Dorsal view of the unfolded cerebellar cortex with cerebellar nuclei. B: Inferior olive. MAO, medial accessory olive; PO, principal olive; DAO, dorsal accessory olive; dm. c.c., dorsomedial cell column; beta, beta nucleus; v.o.l., ventrolateral outgrowth; d. cap, dorsal cap. C: Midsagittal section of the cerebellum. Areas from which electric stimulation evokes cardiovascular responses are shaded. For other abbreviations see text.](image-url)
interpositus (I), and lateral (L) nuclei from medial to lateral. The cerebellum is connected to the brainstem by three fiber tracts: the inferior, middle, and superior cerebellar peduncles. Each small area of the cerebellar cortex receives climbing fiber afferents from a small region of the inferior olive [17, 18, 22–26].

Making a local lesion is a classic means of determining the localization of cardiovascular areas in the cerebellum. Even though an early work revealed no chronic effect of a total ablation of the cerebellum on mean arterial blood pressure [27], more recent studies have revealed that partial cerebellar lesions or cerebellectomy in anesthetized cats caused an augmentation of the baroreceptor reflex [28], a redistribution of cardiac output away from skeletal muscle [29], and a decrease in heart rate [30]. The classic ablation techniques do not distinguish between neurons and passing or terminating fibers. This shortcoming is overcome by the use of kainic or ibotenic acid that destroys only neurons, not fibers. The techniques for detecting functional deficits resulting from lesions have also been improved.

Electrical stimulation is another effective means of determining the functional localization in the cerebellum, but it has the following three disadvantages. First, it does not distinguish neurons from passing or terminating fibers. It should be noted that axons are often excited with a lower threshold than cell somata. A local injection of an excitant amino acid (glutamate or aspartate) that will chemically stimulate neurons, but not pass or terminate fibers, will prevent this from happening. Second, the effect of electrical stimulation may be sensitive to anesthesia. A reversal from excitation in the decerebrate unanesthetized state to inhibition in the anesthetized state has often been observed (see below). In cerebellar cortical stimulation, this reversal can be explained on the basis of neuronal circuit structures of the cerebellum (see Fig. 3 and section IV). In the unanesthetized state, Purkinje cells fire at about 50 Hz so that a stimulation effect is dominated by a decrease in Purkinje cell discharge via basket cells and stellate cells, instead of by an additional firing as a result of stimulation. Cortical stimulation in the unanesthetized state would thus lead to the abolishment of Purkinje cell inhibition from target nuclear neurons (disinhibition) [31]. In the anesthetized state, in contrast, Purkinje cells are spontaneously silent and are readily excited by stimulation, which should enhance the inhibition of nuclear neurons instead of inducing disinhibition. Third, the effect of cortical stimulation may also vary as a result of a slight change of the stimulated site. This is due to the fine mosaic structure of the cerebellar cortex in which a cortical microzone is only 0.3–1.0 mm wide transversely. For a direct stimulation of a relevant group of Purkinje cells in one microzone, the stimulating electrode should be within this microzone. Stimulation at the outside of a microzone would induce an inhibition of Purkinje cells because of the activation of parallel fibers (PFs) and/or mossy fibers (MFs), which in turn inhibits Purkinje cells via basket and stellate cells.

The mapping of neuronal activities correlated with the expression of a certain function is the third means

Fig. 3. Microcomplex structure of the cerebellar neuronal circuit. PC, Purkinje cell; GR, granule cell; PF, parallel fiber; BS, basket cell; ST, stellate cell; GO, Golgi cell; CF, climbing fiber; MF, mossy fiber; LC, Lugaro cell; UBC, unipolar brush cell (modified from [9]).
of identifying functional localization in the cerebellum. This method has widely been applied to the mapping of somatomotor areas of the cerebellum, but has hardly been adopted in the studies of cardiovascular functions because it is rather difficult to correlate Purkinje cell discharges with slowly changing parameters such as mean arterial blood pressure.

Figure 2 shows the frequently investigated cerebellar regions with respect to cardiovascular control since Moruzzi’s pioneering work [1]: the fastigial nucleus (FN), the medial portions of anterior and posterior vermis (medial anterior and posterior vermis), the medial part of the uvula, and the lateral part of the nodulus and uvula (lateral nodulus-uvula).

IV. Neuronal Circuit in the Cerebellum

Histologically, the cerebellar cortex is three-layered (molecular, Purkinje cell, and granular layers) and contains five major types of neurons (Purkinje [PC], basket [BS], stellate [ST], Golgi [GO] and granule [GR] cells) and two major types of afferent terminals (MF and climbing fiber [CF]), as shown in Fig. 3 [8]. Recently, Lugaro cells (LC) [32] and unipolar brush cells (UBC) [33] have been recognized as major elements of the cerebellar cortical circuit.

Afferent fibers arising from various precerebellar nuclei in the brainstem and spinal cord project to the cerebellar cortex as MFs. Their collaterals supply excitatory synapses to cerebellar or vestibular nuclear neurons. The output of the cerebellar cortex is provided solely by the inhibitory axons of PCs, which project to the cerebellar nuclei and VN. The entire cerebellar cortex is also supplied with CFs arising from the inferior olive (IO). A microcomplex consists of these elements and connections, and possibly operates as follows. While input signals flow into a microcomplex along MFs, nuclear neurons generate output signals in a microcomplex. This major signal flow path is superposed by a side path consisting of MFs, GRs and their PF axons, and PCs in series so that the input-output relationship in a microcomplex is modulated by this cortical side path. The CFs, however, convey error signals representing the erroneous performance of the microcomplex and induce long-term depression (LTD), a characteristic type of synaptic plasticity, in PF-to-PC synapses that are active at that time. Thus PF-to-PC synapses involved in an erroneous performance are depressed from trial to trial until only those leading to successful performance remain. This is the likely adaptive mechanism for learning that the cerebellum is presumed to perform [8, 9].

V. Cardiovascular Functions of the Fastigial Nucleus

Electrical stimulations in and around the FN produce a pronounced pressor response as reported in several species: monkey, dog, cat, rabbit, ferret, and rat [34–46]. The stimulation of the rostral FN in unanesthetized cats and dogs also elicits hypertension accompanied by complex behavioral responses, such as grooming, biting, and eating [47]. Following α-adrenergic blockade or sympathectomy, this fastigial pressor response is abolished, indicating that it is mediated by sympathetic nerve activity [36, 37, 48]. The stimulation of the rostral FN induces an increase in the renal sympathetic nerve activity and concomitantly a pressor response [44, 45]. The stimulation of the rostral FN also induces the vasoconstriction in the kidneys, hindlimbs, small intestine and skin [37, 45]. Besides vasoconstriction, vasodilation is induced in the coronary and cerebral beds following the stimulation of the rostral FN [40, 49–53].

Nisimaru and Kawaguchi [44] found in anesthetized rabbits that a localized stimulation of the FN induces an increase in the RSNA and a concomitant increase in arterial blood pressure. These effects were produced by the stimulation of two distinct sites, one being the rostral FN, the so-called fastigial pressor area, and the other the caudal FN. Both the excitatory response of the RSNA and the pressor response disappear after a small electrolytic lesion (about 1 mm² in a cross section) is induced in an effective stimulating focus in the FN. No responses are obtained even with currents as high as 500 μA after this lesion is induced. We therefore suggest that the observed effects of the FN stimulation are due to the excitation of FN neurons that receive Purkinje cell inhibition from the vermal cortex and project to brainstem vasomotor centers.

However, a microinjection of excitatory amino acids (e.g., glutamate, kainate, DL-homocysteic acid, and aspartate) into the rostral FN failed to evoke a pressor response in cats [54], rabbits [55], and rats [56, 57]. Furthermore, following the chemical lesioning of this nucleus, a pressor effect was still evoked by the stimulation of two distinct sites, one being the rostral FN, the so-called fastigial pressor area, and the other the caudal FN. Besides vasoconstriction, vasodilation is induced in the coronary and cerebral beds following the stimulation of the rostral FN [34–46]. The stimulation of the rostral FN in unanesthetized cats and dogs also elicits hypertension accompanied by complex behavioral responses, such as grooming, biting, and eating [47]. Following α-adrenergic blockade or sympathectomy, this fastigial pressor response is abolished, indicating that it is mediated by sympathetic nerve activity [36, 37, 48]. The stimulation of the rostral FN induces an increase in the renal sympathetic nerve activity and concomitantly a pressor response [44, 45]. The stimulation of the rostral FN also induces the vasoconstriction in the kidneys, hindlimbs, small intestine and skin [37, 45]. Besides vasoconstriction, vasodilation is induced in the coronary and cerebral beds following the stimulation of the rostral FN [40, 49–53].

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an awake rat and a decrease of it in an anesthetized one [60–63].

Anatomical data also supports the involvement of FN neurons in cardiovascular functions. Neurons in the rostral FN project to the NTS, which mediates the baroreceptor reflex [64–68], and they also receive from it. Neurons in the rostral FN also project to PBN [69]. Through these connections, the rostral FN may be involved in the control of the baroreceptor reflex because Lisander & Martner [37] showed that the response pattern of arterial blood pressure, heart rate, and regional blood flow to the stimulation of the rostral FN was closely similar to that caused by carotid baroreceptor unloading in anesthetized cats.

On the other hand, the existence of a bilateral projection from the FN to the VN was shown [70–72]. The cerebellar corticovestibular fibers have inhibitory synaptic actions on VN neurons, but the fastigiovestibular fibers have excitatory synaptic actions [8, 73]. A stimulation of the vestibular nerve inhibits both sympathetic nerve discharge and arterial blood pressure, and the effects are abolished by lesions in the medial vestibular nucleus (MVN) or during the stimulation of the posterior lobe of the cerebellum [74, 75]. Thus, the caudal FN is possibly involved in the control of the vestibulo-sympathetic reflex. The stimulation of other cerebellar nuclei (interpositus and lateral) failed to induce any obvious change in arterial blood pressure or heart rate [36, 55].

VI. Cardiovascular Functions of the Anterior Vermis

Many investigators reported a depressor response to the electrical stimulation of the medial anterior vermis in either decerebrate unanesthetized or anesthetized animals [3, 76–79]. In other experiments, medial anterior vermis stimulation evoked a pressor response [1, 28, 80–83]. This variability of the stimulation effects may arise, at least in part, from the different conditions of an animal (anesthetized or not, see above) and also from various stimulus parameters used. For example, in our recent studies of anesthetized rabbits, a brief stimulation of the medial cortical regions of lobules I, II, and III, which induced a marked decrease in the RSNA, caused no noticeable change in arterial blood pressure [79]. Yet when cerebellar stimulation was extended to 10 s, the mean blood pressure decreased. Apparently the accumulation of a certain amount of changes in sympathetic nerve activity is required before cerebellar stimulation leads to changes of mean arterial blood pressure.

The stimulation of the deep white matter of lobules I, II, and III sometimes induces a reversed effect, that is, an increase in the RSNA and a concomitant increase in arterial blood pressure. When an electrical stimulation of lobules I and II evokes such a pressor response accompanied by tachycardia, glutamate intracortical microinjections fail to replicate them. The reversed effects, therefore, are not due to the activation of Purkinje cells and are very likely to be due to the stimulation of MFs, which in turn activate fastigial neurons either directly via collaterals of the stimulated MFs or indirectly via the basket and stellate cells by inhibiting Purkinje cells projecting to the fastigial neurons. From these results, the direct effect of the medial anterior vermis stimulation (lobules I, II, and III) is an inhibition of sympathetic nerve activity and a depressor response.

The effect of medial anterior vermal stimulation may be mediated by Purkinje cells in lobules I, II, and III that project to the rostral FN, the so-called fastigial pressor area. In fact, when the rostral FN stimulation is conditioned by a preceding stimulation of the medial anterior vermis, the test sympathetic nerve activity induced by the stimulation of the rostral FN was effectively depressed (Fig. 4) [44]. It is probable that the medial anterior vermis (lobules I, II, and III) and a small group of neurons in the rostral FN constitutes a microcomplex that acts as a cardiovascular control module of the cerebellum. This microcomplex may adaptively control the baroreceptor reflex as mentioned above (section V).

Nevertheless, since a small group of Purkinje cells directly project from the anterior vermis to PBN and the stimulation of PBN activates Purkinje cells in the anterior vermis [69], there appears to be a medial anterior vermis-PBN microcomplex operating in parallel with the medial anterior vermis-rostral FN microcomplex.

VII. Cardiovascular Functions of the Posterior Vermis

An electrical stimulation of the medial posterior vermis also induces cardiovascular effects, which are either a pressor response and tachycardia or a depressor response and bradycardia [46, 79, 84–87]. We found in anesthetized rabbits that a brief stimulation of the medial vermis of lobules VII and VIII effectively depresses RSNA, and a sustained tetanic stimulation (10 s, 200 Hz) induces a decrease in arterial blood pressure [79, 84]. The most effective site is in the medial portion of lobule VIIa.
stimulated the vagal nerve in rabbit at the level of the cervical region and then recorded evoked field potentials on both sides of the posterior vermis (lobules VII and VIII), with the most prominent potential appearing in the ipsilateral medial vermis of lobule VIIa via CFs [89]. This CF projection is mediated by the contralateral mediocaudal part of the medial accessory olive (MAO), including the beta nucleus [90].

More recently, we reported that CF inputs to the medial vermis of lobule VII convey information from pulmonary stretch receptors and/or receptors from the heart [91]. The medial vermis of lobules VII and VIII, together with the caudal FN and the mediocaudal part of MAO including the beta nucleus, thus forms a microcomplex that serves as a cardiovascular control module. At least one of these microcomplexes is involved in the control of the vestibulo-sympathetic reflex (see section V). The medial posterior vermis (lobules VII and VIII) may also contain another microcomplex that may be involved in controlling respiration [91].

VIII. Cardiovascular Functions of the Uvula (Lobule ix) and Nodulus (Lobule x)

It was reported that the stimulation of the medial portion of the uvula (especially, lobule IXb), either electrically or chemically, induces a depressor response in anesthetized rabbits and cats [46, 55, 86, 92]. However, the effects are reversed in decerebrate unanesthetized rabbits and cats in which the stimulation of the medial uvula induces a pressor response and tachycardia [46, 87, 92, 93]. Anatomically, the uvula and nodulus have extensive afferent and efferent connections with vestibular nucleus [93, 94]. The stimulation of the medial portion of lobule IXb also inhibited neurons receiving baroreceptor inputs in NTS and inhibited neurons mediating a pressor response in the lateral PBN [95, 96]. It was suggested that the medial uvula controls the magnitude and/or direction of heart rate changes during the amygdaloid- and hypothalamic-evoked defense response in the anesthetized rabbit [97]. It was also suggested that the medial portion of lobule IXb acts to alter the plasticity or gain of the baroreceptor reflex during exercise by using mechanisms analogous to those described for vestibulo-ocular reflexes.

Independent of the above cited works, our group discovered a discrete cardiovascular control area in the lateral nodulus-uvula [16, 85] and investigated this area to define its function, as introduced below. This lateral nodulus-uvula is clearly apart from the medial region of the uvula, in which cardiovascular effects are evoked as mentioned above. The lateral and medial regions may contain two different cardiovascular microcomplexes, but a possibility is yet to be excluded that the effects produced by stimulating the two regions arise from the activation of the same microcomplex because of possible cross talk of the electrical stimulation effects via PF or MF branches that may spread transversely. It should be noted that even the effects of chemical stimulation would spread transversely along PFs if the stimuli excite granule cells.

(1) Stimulation of the lateral nodulus-uvula.

In anesthetized rabbits, we induced a decrease in RSNA by stimulating a small region extending more than 1 mm longitudinally through the dorsal nodulus, encroaching the border with the ventral uvula at
2.7–3.7 mm lateral to the midline (Fig. 5) [85]. When the trains of stimulating pulses were sustained over 10 s, arterial blood pressure decreased (Fig. 6A, BP). Concomitantly, the renal arterial blood flow increased transiently and then slightly decreased (Fig. 6A, RBF), but the femoral arterial blood flow increased (Fig. 6A, FBF) [98]. Glutamate microinjection into the localized region of the lateral nodulus-uvula also induces an inhibition of RSNA as well as depressor responses, as shown in Fig. 7 [98].

In decerebrate unanesthetized rabbits, however, an electrical stimulation of the lateral nodulus-uvula with repetitive pulses lasting for several seconds (current intensity less than 100 µA) induced a large transient increase in RSNA followed by an inhibition. These effects are accompanied by a marked increase in blood pressure, a transient decrease in renal arterial blood flow, and an increase in femoral arterial blood flow [98]. This reversal of the pattern of cardiovascular responses shown in Fig. 6 A and B is similar to that observed following the stimulation of the medial region of the uvula [86, 87, 92]. The reversal can be explained by the shift of the dominant stimulus effect depending on the anesthesia mentioned in section III. In the unanesthetized state, the stimulus silences Purkinje cell firing at about 50 Hz by inhibition via stellate, basket, and Golgi cells (see Fig. 3), but in the anesthetized state, stimuli activate otherwise silent Purkinje cells as mentioned in section III. Another explanation so far offered is that the dominance is shifted because of anesthesia between two pathways, which might have opposite effects on brainstem cardiovascular centers [86, 87, 98]. The likely candidates for these two pathways are the one from the superior cerebellar peduncle to PBN and the other from the inferior cerebellar peduncle to VN (see below). However, since there is no evidence that these two pathways have opposite effects on brainstem cardiovascular centers or that they have different sensitivities to anesthesia, author feels that the switching from spontaneously discharging to a silent status of Purkinje cells is a more likely cause for the anesthesia-dependent reversal of the cardiovascular effects of electric stimulation of the lateral nodulus-uvula.

(2) CF inputs to the lateral nodulus-uvula.

The lateralmost region of the uvula receives CFs from
the rostrolateral MAO (rl-MAO), dm.c.c. and/or the d. cap in the contralateral IO [25, 99–101]. We injected horseradish peroxidase (HRP) into the rabbit nodulus, and this revealed six longitudinal zones in the nodulus receiving CFs from five different subdivisions of IO as shown in Fig. 8 [102].

The electrical stimulations of vagal and aortic nerves evoke field potentials in the lateral cortical

Fig. 6. Cardiovascular effect of stimulation in the lateral nodulus-uvula in rabbits. A: Under anesthesia. B: Under the decerebrate unanesthetized condition. BP, arterial blood pressure; RBF, renal arterial blood flow; FBF, femoral arterial blood flow. Horizontal bars show the time when the electrical stimulus was applied [98]. (Reprinted with permission from Elsevier.)

Fig. 7. Effect of electrical and chemical stimulation in the lateral nodulus-uvula. A: Electric tetanic stimulation. B: 0.2 M glutamate (100 nl) was injected through a microsyringe. The stimulation sites (closed circles) on the parasagittal sections of the cerebellum at 4.2 and 3.2 mm lateral from the midline for A and B, respectively. The horizontal bars show the time when stimulus was applied. BP, arterial blood pressure; RSNA, renal sympathetic nerve activity [96]. (Reprinted with permission from Elsevier.)
region of the contralateral nodulus and uvula with a latency of 6.5–19 ms in anesthetized rabbits [103]. An analysis of these field potentials indicated that the lateral nodulus-uvula receives contralateral vagal and aortic afferent signals via CFs [103–105].

(3) MF inputs to the lateral nodulus-uvula.
The nodulus and ventral uvula receive MFs from primary and secondary vestibular neurons [106–109]. Horseradish peroxidase (HRP) injection into the lateral nodulus-uvula in rabbits revealed that this region bilaterally receives MFs from the VN, the prepositus hypoglossal nucleus, Roller nucleus, the intercalatus nucleus, and the medial fasciculus longitudinalis [103].

The electrical stimulation of the vagal nerve also evokes field potentials in the ipsilateral region of the nodusus and uvula with a latency of 6–10.5 ms in anesthetized rabbits. The laminal profile is characteristic of MF responses [103, 110]. However, because no direct anatomical connection from the primary vagal nerve to the lateral nodulus-uvula has been found, these responses are presumed to be mediated polysynaptically. There is electrophysiological evidence indicating that vestibular fibers project to the nodulus and uvula through both the MF and CF pathways [111]. Our results, together with these reported data, suggest that a microcomplex involving the lateral nodulus-uvula receive cardiovascular and vestibular information through CFs and MFs via the brain stem nuclei; some of the VN, the prepositus hypoglossal nucleus, Roller nucleus, and the intercalatus nucleus.

(4) Output from the lateral nodulus-uvula.
That the cardiovascular responses induced by the stimulation of the lateral nodulus-uvula are solely mediated by the sympathetic nervous system is indicated by the results of an injection of hexamethonium, a sympathetic ganglion blocker, into a femoral vein. This injection depressed spontaneous RSNA and concomitantly abolished the effect of electrical stimulation of the lateral nodulus-uvula, which no longer affected arterial blood pressure, renal blood flow, or femoral blood flow [98].

Purkinje cell projections from the nodulus and uvula to the VN were well described in rabbits [64, 112–116], cats [58, 117–120], rats [121], and prosimian primates [122]. Those specifically from the lateral nodulus to the superior vestibular nucleus (SVN), MVN and group y were described in rabbits by using tracing methods [114, 116]. We injected biotinylated dextran amine (BDA, anterograde tracer) iontophoretically into the lateral nodulus-uvula of rab-
bits. We observed that labeled Purkinje cell axons pass within and around the superior and inferior cerebellar peduncles and terminate in the lateral vestibular nucleus (LVN), SVN, MVN, and PBN (Fig. 9) [98]. The cells of infracerebellar nucleus are loosely arranged and may include a part of group y and the lateral nucleus in rabbits [123]. Because of the ambiguous location of these nuclei, projections from the lateral nodulus-uvula to the group y and lateral nucleus may be difficult to separate. When HRP was microinjected into the lateral PBN, retrogradely labeled Purkinje cells were found in the lateral nodulus-uvula [98]. These results indicate that Purkinje cells in the lateral nodulus-uvula project to VN via the inferior cerebellar peduncle and to the lateral PBN via the superior cerebellar peduncle (Fig. 9).

(5) Reflex pathways connected to the lateral nodulus-uvula. Although it is unlikely that these nodulus-uvula-bound vestibular nuclear neurons directly drive the sympathetic preganglionic neurons, numerous neurons directly influencing sympathetic outflow have been found in the caudal medullary raphe nucleus [124, 125] and in the subretrofacial portion of the RVLM (see section II and Fig. 1) [14, 126–129]. Although no direct anatomical connection between vestibular nuclear neurons and raphe nucleus or subretrofacial nucleus neurons, has been found many neurons in these nuclei respond to electrical stimulations of the vestibular nerves [130, 131]. Some neurons in the dorsolateral medullary reticular formation receive vestibular inputs and project to the subretrofacial nucleus [132]. Neurons in the caudal paramedian reticular formation receive inputs from both the vestibular nerve and the carotid sinus nerve [125, 133]. These reticular formation neurons, particularly those in the RVLM, can be considered as forming a potential premotor region for mediating the vestibulosympathetic reflex (Figs. 1 and 11). This reflex is driven by nose-up and nose-down tilting, which affects splenic nerve activity and this effect is abolished by inducing lesions in the MLV and inferior vestibular nucleus (IVN) [134]. This reflex pathway explains the effect of electric stimulations of the vestibular nerve to induce an inhibition of RSNA [74].

The electrical or chemical stimulation of the PBN, especially the lateral PBN, evoked the pressor response, suggesting that the PBN is located upstream of RVLM [13]. The PBN receives afferent inputs from the NTS, which receives primary baroreceptor and chemoreceptor inputs [135–140]. The PBN stimulation also modulates the baroreflex in cats [141, 142]. These observations suggest that the PBN relays the baroreflex that is under the control of Purkinje cells in the lateral nodulus-uvula.

**Fig. 9.** Efferent projections from the lateral nodulus-uvula to the VN and the PBN. Labeled axons and terminal-like deposits in the cerebellum and brainstem are shown following an injection of BDA into the lateral nodulus-uvula in two rabbits (A and B). Line drawings of the normalized sagittal sections of the ipsilateral cerebellum and brainstem. The numbers show distances from the midline in mm. Labeled axons and terminal-like deposits contained in 10 sections (60 µm thick each) are collectively plotted in each illustration. The blue dashed lines in each illustration represent the labeled axons. Red arrows and asterisks (×) show the terminal fields: CG, central gray matter; SCP, superior cerebellar peduncle; ICP inferior cerebellar peduncle; IPB, lateral parabrachial nucleus; mPB, medial parabrachial nucleus; SV, superior or vestibular nucleus; LV, lateral vestibular nucleus; MV, medial vestibular nucleus; IV, inferior vestibular nucleus; IP, interpositus nucleus; L, lateral nucleus; IC, infracerebellar nucleus (modified from [98]).
Previous anatomical studies on rabbits and rats showed that the SVN, MVN, and inferior vestibular nucleus (IVN) project to the PBN and KFN. A recent study of rabbits and rats demonstrated that the SVN and KFN reciprocally project to the SVN, the dorsal aspect of the rostral MVN, the caudal MVN, the pars beta of the LVN, and the IVN [143].

The lateral nodulus-uvula is connected to these brainstem nuclei mediating the vestibulosympathetic reflex and baroreflex pathways through Purkinje cell projections to the PBN. The lateral nodulus-uvula, together with the small groups of PBN and VN neurons and a small group of neurons in the rl-MAO and/or dm.c.c., possibly forms cardiovascular microcomplexes.

(6) Adaptive control function of the lateral nodulus-uvula. To identify the roles of the lateral nodulus-uvula in arterial blood pressure control, we imposed anesthetized (with α-chloralose plus urethane) rabbits with head tilting at a 30° upward position from one 30° downward. This stimulus caused an inhibition of RSNA and a concomitant decrease in arterial blood pressure. The RSNA recovered to the control level within 2–4 s, but arterial blood pressure recovered gradually to the control level within about 20 s (Fig. 10) [144]. It appears that under anesthesia, the upward head tilting stimulates the vestibular labyrinth, and this activates VN neurons. The vestibulosympathetic reflex evoked in this way inhibits RSNA, which leads to a decrease in arterial blood pressure. The later gradual recovery of the RSNA and arterial blood pressure may be due to the baroreceptor reflex [145, 146]. Since Purkinje cell firing stops in anesthetized rabbits, the effects of head tilting under the anesthetized condition (Fig. 10A) may represent the basic operation of the combination of the vestibulosympathetic and baroreceptor reflexes in the brainstem, which generally are insensitive to anesthesia (see Figs. 3 and 11) [74, 145, 146].

In awake rabbits, head tilting at a 30° upward position from one 30° downward, initially induced an inhibition of RSNA, which was immediately reversed to a transient increase. Arterial blood pressure changed in a similar time course, initially decreasing and recovering to the control level within 3–5 s. After a bilateral destruction of the lateral nodulus-uvula, a similar head tilting caused an immediate large increase in RSNA without the early inhibition, which was sustained at a high level. Arterial blood pressure increased transiently, and then decreased; thereafter it was maintained at a level lower than in the control (Fig. 10B) [144]. These results show that the timing and duration of the transient increase in the RSNA during the head tilting are controlled by the lateral nodulus-uvula, in which Purkinje cell firing changes in response to vestibular and baroreceptor inputs via mossy and climbing fibers (Figs. 3 and 11). This control is apparently important in everyday life because...
Conclusions and Perspectives

This article reviewed the presently available evidence for the microcomplex representation of cardiovascular functions in the cerebellum. Five major cardiovascular microcomplexes are in the cerebellum. The first one includes the medial anterior vermis (lobules I, II, and III) and the rostroventromedial portion of FN, the so-called fastigial pressor area, and the second includes the medial posterior vermis (lobules VII and VIII) and the caudomedial portion of FN. A third is formed by the medial anterior vermis with PBN, but not FN and a fourth includes the medial uvula and NTS/PBN. The fifth one includes the lateral nodulus-uvula and PBN/VN. Neuronal circuits are best analyzed for this fifth module.

The major functions of these multiple microcomplexes are considered to be adaptive controls of the vestibulosympathetic reflex and the baroreflex. On the basis of the aforementioned connection data, the vestibulosympathetic and baroreflexes may form a two-degrees-of-freedom control system that combines feedback and feedforward control systems (Fig. 11). The feedforward pathway from the vestibular labyrinth to the VN and the feedback pathway from baroreceptors to the NTS and PBN converge on the common controller part in the RVML. This combined control system maintains the mean arterial blood pressure against head movements and any perturbation of blood pressure under adaptive control by the five cardiovascular microcomplexes.

The cardiovascular dysfunctions in motion and space sicknesses may be caused by a failure of control mechanisms associated with the lateral nodulus-uvula. Furthermore, investigations of the lateral nodulus-uvula will be important in elucidating the integrative neuronal mechanism of the central nervous system functions because it is the crossroad of autonomic, vestibular, and cerebellar signals.

Despite the multiple-sited involvement of the cerebellum in cardiovascular control, another region of the flocculus has recently been found to be related to cardiovascular control [147]. The completion of the entire functional map of the cerebellum and the functional specification of individual microcomplexes is a goal of research on cerebellar cardiovascular control functions.

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