Cerebellar control of visceral responses–possible mechanisms involved

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It seems reasonable to assume that cerebellar autonomic control operates according to similar principles as those utilized in the somatomotor coordination. The unique and very uniform neuronal architecture throughout the cerebellum speaks in favour of such a view.

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To effectuate coordination of somatomotor movements the cerebellum receives information from a variety of somatic sensory receptors and from higher centers as well. Afferents from visceral organs have been found to project on the cerebellum, converging on the same population of cerebellar neurons as the somatic afferents. Moreover, background reflex activity modifies autonomic response to cerebellar stimulation. Rebound phenomena are seen also in association with autonomic influences e.g. on the bladder. In addition, one and the same cerebellar stimulation may influence both the somatomotor and autonomic components of combined patterns, like those seen in sham rage, defecation, or the oral behaviour, which was predominantly associated with cardiovascular adjustments. Many situations, like physical activity and emotional behavioural patterns require concomitant integrations of complex somatomotor and autonomic events, which must be well synchronized and timed to occur in proper sequences. Presumably, the cerebellum participates in such complex coordinations and the present review lend support to such a view, illustrating some of the principles for the cerebellar modulation of combined autonomic and somatomotor adjustment.

The cerebellum is a subconscious part of the brain that serves as a relay station for unconscious proprioception, balance, coordination and control of certain autonomic functions. These are not under the direct control of will. Recent information has confirmed early results indicating an involvement of the cerebellum in functions beside its well-known control of somatomotor mechanisms. For example, cerebellar influences on autonomic regulation, especially concerning cardiovascular mechanisms, have been demonstrated. Further, there are reports of behavioural and “emotional” effects following cerebellar lesions and stimulations.

From the rostral fastigial pole, powerful and well reproducible pressor responses can be elicited by electrical stimulation1. The results indicate that this pressor area, in addition to its cardiovascular influences, is also involved in several other aspects of autonomic regulation. For example, colonic and small intestinal motility2 and defecation; micturition and different reflex arcs involved in gastric motor control can be markedly influenced by fastigial stimulation. Thus, both the parasympathetic pathways, vagal and sacral and the sympathetic inhibitory nerve supply and hormonal link of the sympatho-adrenal system can be modulated. This latter example of hormonal involvement is in agreement with demonstrations that fastigial stimulation can affect anti diuretic hormone (ADH) secretion as well. In addition, oral behaviors can be elicited from the fastigial pressor area3, 4.

It, therefore, appears as if a great variety of autonomic adjustments can be induced from a quite restricted section of the cerebellar efferent outflow, involving virtually all links of the parasympathetic and sympathetic adrenal systems and, consequently, their subordinated effector organs. However, these different autonomic effects, which can almost all be induced from the same electrode position in the

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fastigial nucleus, do not form the same type of regular as well integrated response patterns as those which can be elicited from hypothalamic “feeding area” or defense area. While these latter responses are always in the same direction, it seems as if fastigial neurons exert rather a modulating influence on autonomic control in general, often damping prevailing activity when this is high but exerting a facilitating influence when activity is initially low. Such a type of influence largely seems to hold for the gastrointestinal system, while the fastigial influence on sympathetic activity to the cardiovascular system appears to be mainly of a facilitatory nature. This is so, even when the cardiovascular sympathetic discharge is enhanced by baroreceptor unloading or defense area stimulation. This concentration of a variety of vegetative and hormonal influences to a very restricted part of the fastigial nucleus is in line with observations that the fastigial neurons seem to be aggregated in colonies related performance.

The cerebellar cortex and nuclei are closely related. The cortical output, the Purkinje cell axons, appears to exert a uniformly inhibitory influence on the cerebellar and vestibular nuclei, which together give rise to the only efferent pathways from the cerebellum. The finding that widespread vegetative effects can be elicited from the fastigial nucleus can be taken as evidence for an involvement of the corresponding sections of the complex cortical machinery in the modulation of autonomic functions. To begin with, at least, the general principles of such cerebellar autonomic influences are more easily mapped out, and analysed with respect to involvement of different pathways, by utilizing proper excitation of the stations for the efferent neurons i.e. cerebellar nuclei. It is obviously more difficult to perform, and to analyse, stimulations in the cerebellar cortex, partly because Purkinje cells subserving a particular function may be widely dispersed, partly because Purkinje cells whose functional involvement is a different one. Moreover, it has been suggested that the main operative reflex loop for cerebellar function is the direct pathway via the mossy fibers to the nuclear neurons and their efferent connections, leaving the superimposed loops of the cerebellar cortex to a secondary, but of course, highly important modulating role. If so, it would be easier to trace at least some of the basic cerebellar effects by utilizing nuclear stimulations.

The observation that fastigial stimulation may influence a variety of autonomic reflexes suggests a cerebellar involvement in their normal control, but does not tell exactly how this regulation is performed. Electrical stimulation within the fastigial nucleus, even though a necessary step in exploration of the cerebellar autonomic control mechanisms, no doubt produces a very stereotyped and poorly differentiated excitation of fastigial neurons and adjacent nervous pathways. Such excitations are, for natural reasons, far from delicate and complex neuronal activity patterns displayed during normal cerebellar operation. In the physiological situations the fastigial neurons show a pattern of continuous discharge, which is sculptured by inhibitory influences from the likewise continuously firing Purkinje cells, in turn modulated by the nature of incoming information, which also initiates the fastigial discharge. By increasing or decreasing the rate of Purkinje cell discharge, on the basis of the computed afferent input, the activity in the fastigial neurons can be reduced or increased, respectively. This provides a sensitive mechanism for a continuous in vivo modulation of reflexes in both excitatory and inhibitory directions, even though a more or less uniform suppression of a given autonomic reflex may be the result of fastigial stimulation.

Towards such a background some apparently incongruent observations in the present review may be explained. For example, it may seem inappropriate that the stimulation of the same fastigial area induces oral behaviours and even eating, but also an inhibition of the vago-vagal relaxatory reflex. This latter reflex normally adjusts the stomach for food reception and is facilitated during eating. However, as mentioned above, an artificial fastigial stimulation may well lead to a stereotyped uniform inhibition though the normal function of the cerebellum may rather be to adjust the vago-vagal relaxatory reflex to a suitable level. It may also be so that the fastigial suppression of this reflex and the oral behaviours are initiated by different pools of fastigial neurons indiscriminately excited by electrical stimulation, a pattern of activation that is perhaps not normally present.

A similar line of reasoning may be applied in accounting for the unexpected observation that the fastigial stimulation, known to induce sham rage in thalamic animals, may suppress e.g. the cholinergic vasodilator fibre activation of the hypothalamic defense reaction while exciting the adrenergically mediated links of this reaction. From these observations it seems probable that the cerebellum is
involved in the coordination of the defense reaction. This may take the form of an adjustment of the discharge in the cholinergic vasodilator fibers to suit the associated pattern of behaviour so that the neurogenic dilator influence becomes more or less restricted to active muscle groups. In fact, the cholinergic muscle vasodilatation, when evoked by conditioned stimuli, seems to particularly appear in muscles directly engaged in movements. Such a hypothesis for cerebellar modulation of the neurogenic vasodilation, with suppression of the response until muscles become activated, seems to fit well also with a model for cerebellar somatomotor control. Cerebellum rather than turning on “correct” movements turns off “incorrect” ones.

Also from another point of view, the lack of generalized facilitation of the defense reaction from the fastigial nucleus may at first sight appear unexpected. Considering the neuronal patterns in the cerebellum one would expect largely opposite effects from cortical and nuclear stimulations. Accordingly, an all out facilitation of the defense reaction should follow upon fastigial stimulation, since cortical stimulation induces a generalized suppression. However, a closer look into the cerebellar neuronal connections may explain why this was not the case. During more widespread cortical stimulation some of the white matter is likely to be excited as well, due to extensive folding of the cerebellum. Therefore climbing and mossy fibers, which both send excitatory collaterals to the nuclear neurons, may be antidromically excited in addition to the stimulation of the Purkinje cell axons. The net result on the fastigial neurons may end in part as excitatory one, during cortical stimulation when applied in such a way.

Importance of background reflex activity—As mentioned above, it is most likely that the cerebellum exerts its autonomic influence by modifying reflex relay stations and higher centers controlling autonomic neuroeffectors. If so, the prevailing reflex activity must be of utmost importance for determining the response to cerebellar stimulation, which also appears to be the case. Thus, cardiovascular, gastrointestinal and bladder responses are all very much dependent on the initial level of autonomic activity and impinging reflex influences. For example, quite different gastrointestinal responses occur upon fastigial stimulation, depending on whether intestino-intestinal (gastric) inhibitory reflexes are operating or not. When such reflexes are active, they are subject to fastigial suppression leading to motility decreases. If, however, no such spinal sympathetic reflex activity is going on, the same fastigial stimulation may now depress motility by enhancing the inhibitory adrenergic discharge. Hence, when the cerebellar influence on autonomic function is studied, it is of utmost importance to have full control of and insight into the level of activity in both, the various efferent autonamical pathways and the subordinated effector systems. Otherwise the results are likely to be very confusing, apparently lacking all regularity and order.

Level of integration—Cerebellar interaction with autonomic regulation can theoretically take place at any level of the nervous system, from the peripheral receptors to the cerebral cortex. It is, in fact, quite likely that there are several levels of integration, further, differences between various autonomic reflexes may occur, which must be kept in view when the results are interpreted.

It is a priori unlikely that autonomic effects from the cerebellum are due to a descending, direct interaction with neurons or receptors outside the central nervous system, even though the principle of efferent neurogenic modulation of receptor sensitivity is generally accepted. Such a view is further supported by the following observation: First, fastigial stimulation was found to modulate the defecation reflex equally efficiently whether the reflex was induced by a “physiological” excitation of rectal receptors or by afferent pelvic nerve stimulation. Second, fastigial stimulation was found to influence all autonomic reflexes tested, with one notable exception; mechanical stimulation of the intestinal mucosa elicits an intestinal vasodilatation, which is fairly unique by being conveyed via strictly intramural reflex connections, and this type of extra spinal autonamic reflex was not influenced by fastigial stimulation.

Cerebellar influences on spinal or/and bulbar autonomic structures appear as probable levels for interaction. In fact, several autonomic reflexes that relay on these levels are liable to cerebellar modulation. For example, the cerebellum can influence cardiovascular, micturition, and gastric reflexes. Further, these mentioned modulations are all present in animals subject to decerebration at pre- or intercollicular levels showing that these particular cerebellar influences are not relayed at CNS centers.
cranial to mesencephalon. Also, the fastigial pressor response does not require higher levels of the nervous system since decerebration does not abolish the blood pressure increase upon fastigial stimulation\textsuperscript{6}.

There are, however, indications that higher autonomic centers, like the hypothalamus and the limbic system, may be exposed to cerebellar influences concerning the vegetative functions that are integrated at these levels. Thus, the cerebellum can influence ADH release\textsuperscript{3} and also induce sham rage\textsuperscript{16}. Further, cardiovascular and gastric responses elicited from the hypothalamus can be influenced by cerebellar stimulation, as is the case with the autonomic components of the hypothalamic defense reaction. However, an interaction with relay centers of the ascending or descending pathways can, of course, not be excluded in these cases. Thus, the fibre system that controls the sympathetic cholinergic vasodilator fibers has synapses both in the mesencephalon and in the spinal cord. Further indications of a cerebellar-hypothalamic interrelation come from observations that some cardiovascular responses elicited by cerebellar stimulation are abolished by precollicular decerebration or by diencephalic coagulation.

Even if the results from the studies mentioned above clearly demonstrate an interaction between limbic-hypothalamic influences and cerebellar influences, they cannot be taken conclusive evidence for the assumption that some cerebellar effects are really relayed at hypothalamic and limbic levels. The mentioned interaction may well take place in centers e.g. at bulbar levels whose functions are affected by and dependent on both types of influences.

There is however, neuroanatomical evidence for connections between the cerebellum and the hypothalamus or/and the limbic system. Such connections have been demonstrated both with electrophysiological methods and with histological studies.

It is of considerable interest to learn as to how the fastigial induction of the oral behaviour is effectuated, and which nervous structures are involved in it. In case the cerebellum is capable of learning and memorizing patterns of somatomotor performance as proposed, fastigial stimulation\textsuperscript{17} might have activated learned sequences of movements involved in oral behaviour. It is however, difficult to understand how such complex and well-coordinated motor performances are integrated. A more reasonable explanation seems to be that the fastigial neurons exert a general facilitating influence on centers that normally initiate and integrate oral behavioural patterns e.g. the hypothalamic feeding area, the limbic system etc. The amygdala may here be of particular interest since oral behaviour can be particularly easily induced by stimulation in this region, and it was shown that the amygdala receives ascending projections from the fastigial nucleus\textsuperscript{18}. Also, a fastigial facilitation of bulbar relay centers may be of relevance for the oral responses, since even rather complex motor performances can be integrated at these lower levels of the neuraxis\textsuperscript{19}. The incitement of oral behaviour by unpleasantness sensations, induced by cerebellar stimulation, is a third possibility, which, however, appears unlikely since self-stimulation can be obtained from the same areas that produce these response patterns.

Parallels to somatomotor functions—It seems reasonable to assume that cerebellar autonomic control operates according to similar principles as those utilized in the somatomotor coordination. The unique and very uniform neuronal architecture throughout the cerebellum speaks in favour of such a view.

To effectuate coordination of somatomotor movements the cerebellum receives information from a variety of somatic sensory receptors and from higher centers as well. Afferents from visceral organs have been found to project on the cerebellum, converging on the same population of cerebellar neurons as the somatic afferents\textsuperscript{20}. Moreover, background reflex activity modifies autonomic response to cerebellar stimulation. Rebound phenomena are seen also in association with autonomic influences e.g. on the bladder. In addition, one and the same cerebellar stimulation may influence both the somatomotor and autonomic components of combined patterns, like those seen in sham rage, defecation, or the oral behaviour, which was predominantly associated with cardiovascular adjustments. Many situations, like physical activity, emotional behavioural patterns require concomitant integrations of complex somatomotor and autonomic events which must be well synchronized and timed to occur in proper sequences. Presumably, the cerebellum participates in such complex coordinations and the present review lends support to such a view, illustrating some of the principles for the cerebellar modulation of autonomic and somatomotor pathways; and neurotransmitters and receptors involved.
Neurotransmitters in higher centre and spinal cord—The cerebellum is interconnected to the reticular formation, raphe nucleus and locus ceruleus complex and nucleus tractus solitarius, in the brain stem which serves as the switch box controlling most autonomic functions for example micturition and defecation.

The neurotransmitters include serotonin and norepinephrine. Serotonin containing neurons have their cell bodies in the midline raphe nuclei of the brain stem and project to portions of the hypothalamus, the limbic system, the neocortex, the cerebellum and the spinal cord. The cell bodies of the norepinephrine containing neurons in the brain are located in the locus ceruleus and other nuclei in the pons and medulla. These constitute the noradrenergic locus ceruleus system, that descends into the spinal cord and enters the cerebellum.

Receptors in peripheral organs—Sympathetic postganglionic neurons also release norepinephrine, neuropeptides such as neuropeptide Y and ATP. Receptors for norepinephrine include α and β adrenergic receptors.

Neurons of the enteric nervous system release not only acetylcholine and nor epinephrine but also serotonin, ATP and a variety of peptides as neurotransmitters. The effects of cerebellum on the gastrointestinal tract are mediated by these neurotransmitters.

Autoregulatory function of cardiovascular responses are regulated from the medulla during hypotension and shock. The responses are modified by input from the cerebellar granule cells.

Summary and conclusions—The present review has been carried out to investigate control of autonomic functions. Stimulation of the cerebellar fastigial nucleus influences bulbo spinal mechanisms via the axonal connections of the nuclear neurons. This cerebellar nucleus receives its cortical connections from the medially located vermis region. The fastigial nucleus contains in its rostral pole a restricted area which upon stimulation produces pressor responses and from which also a number of other autonomic influences and behavioural changes could be induced, as outlined below:

Fastigial stimulation suppresses the cholinergic vasodilatation in skeletal muscle elicited from the hypothalamic defense area. This suppression is due to a fastigial modulation of activity in the central pathways mediating the cholinergic vasodilatation. The adrenergic links of the defense reaction on the other hand, potentiated by fastigial stimulation. Hence, the fastigial impact on the defense reaction was a differentiated one implying both facilitation and inhibition.

Intestinal motility is influenced from the fastigial nucleus, but differently so in laprotomy compared to that without any abdominal surgery or irritation. After laprotomy both excitatory and inhibitory jejunal responses have been recorded while the ileum and colon uniformly responded with contraction. Abdominal surgery reflexly induces inhibitory adrenergic discharge to the gastrointestinal tract. The contractions recorded in the ileum and the colon following fastigial stimulation are in all likelihood due to a fastigial suppression of such prevailing inhibitory adrenergic discharge. A similar fastigial suppression of sympathetic gastrointestinal discharge is obtained when intestino-intestinal inhibitory reflexes are induced by intestinal distention or by afferent mesenteric nerve stimulation.

In contrast, when intestinal motility is recorded atraumatically fastigial stimulation induced inhibition of ileal motility, reflects a fastigial facilitation of sympathetic activity to the intestine. If, however, a high background of gastrointestinal discharge is present due to abdominal trauma, then fastigial stimulation instead suppressed this sympathetic discharge, hereby changing the ileal motility response pattern into one of excitation.

Fastigial stimulation is potent in influencing both somatomotor and autonomic reflex adjustments involved in defecation. Thus, the straining movements, as well as the parasympathetically conveyed increases in colonic blood flow and motility are strongly suppressed by concomitant fastigial stimulation. The micturition reflex as well is influenced from the fastigial nucleus, but the direction of the responses depended on the stimulation site in the fastigial nucleus. Further, these responses to fastigial stimulation are also influenced by background bladder tone, suppression occurring when the parasympathetic reflex activity was initially high, and vice versa. They are predominantly due to a fastigial modulation of parasympathetic discharge to the bladder.

Gastric motility is affected from the fastigial nucleus in various ways depending, in each case on prevailing activity in the three effenter autonomic links, which affect gastric motility. Inhibitory
The visceral muscles tone is also controlled by the lateral motor cortex involving the dentate nucleus for equilibrium and tone and the lateral system from the ventrospinal and laterospinal that control posture, functional somatomotor pathways exist, one medial and lateral, the midline and lateral system, the midline system modulating the basal tone or static tension and the lateral fine tuning the phasic and dynamic component of muscle tone (Fig. 1). However, the cerebellar influence is not only confined to such selected autonomic responses closely associated with e.g. particular somatomotor adjustments such as the defense reaction, the feeding response, the act of defecation etc., but appears to affect virtually all types of autonomic mechanisms, including reflexes engaged in bulospinal, “homeostatic” mechanisms and resulting in cardiovascular, gastrointestinal or urinary bladder adjustments. Probably, the cerebellar influence takes the form of a modulating and fine-adjusting influence, which is, exerted mainly at spinal and bulbular levels, but it appears likely that cerebellar autonomic interactions may occur also at higher levels by means of fastigial projections on hypothalamic and limbic structures.

**Fig. 1**—Hypothetical diagramme describing circuitry involved responses could be initiated by a fastigial increase in adrenergic fibre discharge or/and in adrenal catecholamine release. Excitatory responses could be induced by an increase in vagal cholinergic fiber discharge, but also by a fastigial inhibition of a prevailing reflex activity in the vagal relaxatory fibers. Further, fastigial stimulation could induce gastric excitatory responses also by suppression of a prevailing sympathetic inhibitory fiber discharge as in the intestine, whenever, such activity was present as induced by abdominal surgery or intestinal distention.

Under conscious awareness fastigial stimulation evokes a well-coordinated oral behaviour, such as licking, grooming, biting and chewing, sometimes even eating. As under anesthesia, this topical fastigial stimulation induced pressor responses as well, but the oral behaviour is not accompanied by any conspicuous adjustments of gastric function in terms of either motility or acid secretion. Histological examination revealed that the responsive cerebellar area i.e. the rostral fastigial pole was the same for the behavioral changes as far most of the autonomic responses reported in this review.

It is thus possible to induce a variety of autonomic effects from a restricted fastigial area, involving virtually all links of the parasympathetic system and the sympathetic system including the adrenals. The results therefore indicate that the cerebellum is involved in the regulation of a variety of autonomic functions, perhaps according to principles, similar to those valid for cerebellar somatomotor control. Two functional somatomotor pathways exist, one medial the ventrospinal and laterospinal that control posture, equilibrium and tone and the lateral system from the lateral motor cortex involving the dentate nucleus controlling the distal muscles for fine movements. The visceral muscles tone is also controlled by the

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