The Cerebellum (2023) 22:1045–1051
https://doi.org/10.1007/s12311-022-01480-7

CEREBELLAR CLASSIC

The Discovery of the Monoaminergic Innervation of the Cerebellum: Convergence of Divergent and Point-to-Point Systems

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Published online: 23 September 2022

Abstract
This *Cerebellar Classic* highlights the landmark discovery of the innervation of the cerebellar cortex and cerebellar nuclei by noradrenergic and serotoninergic axons emanating, respectively, from the locus coeruleus and the raphé nuclei. Since then, modulation of the activity of cerebellar neurons by the monoamine systems has been studied extensively, as well as their reorganization and modifications during development, plasticity, and disease. The discovery of noradrenergic and serotoninergic innervation of the cerebellum has been a crucial step in understanding the neurochemical relationships between brainstem nuclei and the cerebellum, and the attempts to treat cerebellar ataxias pharmacologically. The large neurochemical repertoire of the cerebellum represents one of the complexities and challenges in the modern appraisal of cerebellar disorders.

Keywords Cerebellar afferents · Monoamines · Norepinephrine · Serotonin · Developmental plasticity

Divergent or "global" neural systems imply situations, whereby a relatively small number of neurons innervate a much larger number of terminal domains, in contrast to so-called "point-to-point" systems, where each neuron only contacts a few target nerve cells [1]. Since the time of Ramón y Cajal, the cerebellum had classically been considered a point-to-point system. With the discovery in the 1960s of the cerebellar monoaminergic innervation by neurons of the locus coeruleus and the raphé nuclei, the cerebellum has become a structure where "point-to-point" and "global" neural circuits converge. Moreover, monoamines may exert a widespread effect on neurons besides those receiving physical synaptic appositions—that is, they may subserve a paracrine function [2].

In the human brain, the locus coeruleus contains an average of 50,000 noradrenergic neurons [3, 4], while in rodents it contains about 3,000 cells [5]. The dorsal raphé nuclei of the human brain contain around 130,000–200,000 serotoninergic neurons [6], while that number in rodents is about 8,000–9,000 cells [7, 8]. Thus, the thousands of neurons in both these anatomical systems influence the physiological activity of extensively divergent domains that comprise several billion neurons, from the telencephalon to the spinal cord.

The *Cerebellar Classic* [9] by the pioneer Swedish neuroscientists Nils-Erik Andén, Kjell Fuxe, and Urban Ungerstedt revisited here has broadened the sources of afferent input to the cerebellum beyond the "traditional" climbing and mossy fibers. It has also paved the way for studies on the fate and reorganization of cerebellar monoamine systems in human diseases [10] and in experimental models of cerebellar degeneration [11–21], as well the elucidation of phylogenetic [22, 23], ontogenetic [24–26], developmental plasticity [27–29], and reinnervation issues [30].

Andén and colleagues [9] studied central monoamine neurons and their unmyelinated axons by means of fluorescence histochemistry after removing the cerebral cortex and cerebellum by suction with a fine glass cannula. In biochemical measurements, they found the mean concentration of norepinephrine in the normal rat cerebellum to be 0.18 μg/g, representing approximately 8% of the total brain amount; the mean concentration of serotonin was 0.07 μg/g or about 2.5% of the total brain amount. The authors concluded that

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most, if not all, norepinephrine nerve terminals in the cerebral cortex and the cerebellum belonged to axons originating from noradrenergic cell bodies primarily located in the reticular formation of the medulla oblongata and the pons. They further articulated the idea that the same noradrenergic neuron may innervate both the cerebral cortex and the cerebellum. That last organizing principle of the anatomical projections of coerulear noradrenergic neurons was subsequently confirmed with the identification of collateral axons in the cerebellar cortex, the cerebellar nuclei, and other areas of the central nervous system, including the cerebral cortex, the diencephalon, and the spinal cord [31, 32].

The monoaminergic innervation of the cerebellar cortex comprises norepinephrine- and serotonin-containing axons (Fig. 1) [9, 31]. The origin of the noradrenergic projection lies in neurons of the dorsal part of the locus coeruleus [33–35], the nucleus subcoeruleus, and fields A5/A7 [22, 36, 37]. Furthermore, horseradish peroxidase (HRP) tracing experiments in rats showed heavy innervation of the locus coeruleus by all raphé nuclei, in addition to many extra-raphé brainstem sources [38], suggesting close interactions between the two main brainstem monoaminergic nodes that target the cerebellar circuitry. Using fluorescence histochemistry, researchers have found that the noradrenergic innervation of the cerebellar cortex is more pronounced than its serotoninergic innervation [31]. Electron microscopic studies have shown that, in the rodent cerebellum, norepinephrine-containing axons are apposed to Purkinje cell dendrites [39, 40].

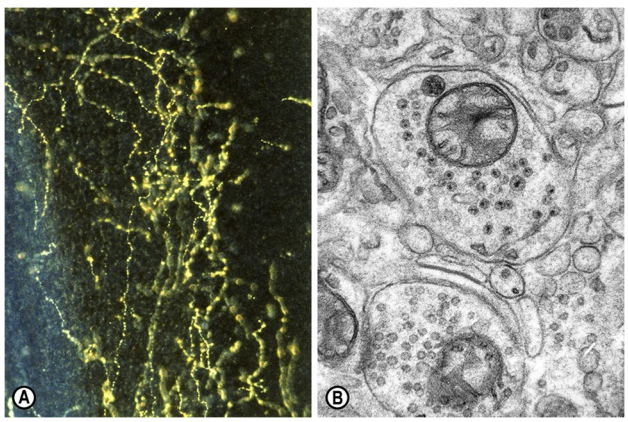

Fig. 1 (**A**) Serotonin-immunoreactive fibers in the mouse cerebellum, displaying their typical axonal varicosities. Sternberger peroxidase-antiperoxidase (PAP) method, dark-field illumination, ×40 [18]. (**B**) Electron micrograph of a monoaminergic varicosity or bouton *en passant* in the molecular layer of the cerebellum of a "Purkinje cell degeneration" (*Agtpbp1*^{pcd}/*Agtpbp1*.^{pcd}) mutant mouse, containing small granular vesicles (40–60 nm in diameter) and a large granular vesicle (90–110 nm in diameter). Potassium permanganate ($KMnO_4$) fixation method, ultrathin section stained with uranyl acetate and lead citrate, ×24,000 [16]

Physiological experiments have indicated a neuromodulatory role for norepinephrine [41, 42] and serotonin [43], both adjusting the activity of other synaptic inputs to the Purkinje cells rather than exerting a strict excitatory or inhibitory effect. The presence of α and β adrenergic receptors on Purkinje cells suggests the existence of bidirectional mechanisms of regulation that allow noradrenergic afferents to refine the signals arriving at Purkinje cells, including the parallel fiber input, under specific arousal states or during motor skill learning [44]. Cerebellar catecholamines, especially in the lateral cerebellar nucleus, might modulate certain aspects of cognitive and affective behavior, such as sensorimotor integration, associative fear learning, response inhibition, and working memory [45].

Serotonin-containing axons originate in neurons of the dorsal raphé nuclei of the pons and of the medullary and pontine reticular formation [46–48], and are distributed throughout the cerebellar cortex of the rat [9, 31, 48, 49] and the mouse [18]. A small contingent of serotonin terminals belong to typical mossy fibers; these are confined to the granule cell layer and establish synapses on dendrites of granule cells [24, 50]. The vast majority of serotonin nerve terminals belong to finer beaded axons of the so-called "diffuse system" and are distributed to all cerebellar cortical layers [50]. Serotonin axon terminals innervate the dendrites of Purkinje and granule cells; the parallel fibers; as well as basket, stellate, and Golgi cells and neurons of the cerebellar nuclei [24, 46, 48, 50]. Iontophoretic application of serotonin and electrophysiological stimulation of the raphé nuclei modulate the firing of Purkinje cells [43, 51–53]. Moreover, serotonin modulates the glutamate-induced excitation and the γ-aminobutyric acid (GABA)-elicited inhibition of Purkinje cells [54, 55].

With regard to the "third monoamine," dopamine (3,4-dihydroxyphenethylamine), the cerebellum had not been considered an elective dopaminergic region, and the very small amounts of dopamine detected in it were thought to represent an intermediary product in the metabolism of norepinephrine [56]. Later studies have suggested the presence of a small dopaminergic contingent in the cerebella of rodents and primates [57–59], as well as the expression of dopamine D_1–D_5 receptors and dopamine transporters [21]. Still, the density of dopamine D_2 receptors in the cerebellum represents about 1% of their density in the striatum [60]. Although unequivocal evidence on the functional role of a cerebellar dopaminergic system is still lacking, its involvement in associative and projective circuits has been discussed [61].

This *Cerebellar Classic* highlights a milestone in the elucidation of the neurochemistry of the cerebellum, whose main transmitters and neuromodulators also include glutamate, GABA, acetylcholine, nitric oxide, endocannabinoids, and neuropeptides. This large neurochemical arsenal is one the features of the cerebellum; they are involved in the numerous motor/non-motor functions of the cerebellum and have variable impacts on cerebellar ataxias.

Appendix

Monoamine Pathways to the Cerebellum and Cerebral Cortex

From previous work[1] it is known that the noradrenaline (NA) and 5-hydroxytryptamine (5-HT) nerve terminals of the rat cerebral cortex derive from axons which originate from NA and 5-HT cell bodies in the lower brain stem and ascend mainly in the medial forebrain bundle. After axotomy retrograde changes occur in those cell bodies and monoamines accumulate in the neuron proximal to the lesion[2,3]. Using these principles the effect of removal of the cerebral cortex and cerebellum on the central monoamine neurons has been studied with the help of the histochemical fluorescence method[4,5].

Adult male Sprague-Dawley rats were used both in the histochemical and biochemical experiments. In about half of the animals used for histochemistry the cerebral cortex was removed uni- or bilaterally. In some cases the cortex was transversely cut at the level of anterior commissure. In these operations the scull was opened and the dura removed so that as much as possible of the cerebral cortex was exposed. The lesions were performed by means of suction with a fine glass cannula. In the other animals taken for histochemistry as much as possible of the cerebellum was removed in an analogous way. All operations were performed in ether anaesthesia. At different time-intervals after the operation the animals were killed by decapitation under light chloroform anaesthesia. The various parts of the brain were dissected out, freeze-dried, treated with formaldehyde gas for 1 h, embedded, mounted and examined as described previously[6,7].

In the biochemical experiments the concentration of NA and 5-HT in the cerebellum, the cerebral cortex, the amygdala and the hippocampus were determined spectrophotofluorimetrically after cation exchange chromatography[8–10].

Removal of cerebral cortex. Usually more than $^2/_3$ of the cortex were removed. In most cases the basal layers were preserved. At all time-intervals (1–5 days) studied there was a marked accumulation of NA and 5-HT in axons running fronto-occipitally in the cingulum frontal but not occipital to the place of the lesion (Figure 1). The axons could be traced frontal for several mm and were seen to enter the cingulum just frontal to the septal area.

The axons were very thin and appeared to be unmyelinated. In no case did monoamine-containing cell bodies appear in the remaining parts of the cortex. Sometimes the damage penetrated also into the subcortical structures. In these cases an accumulation of catecholamines (CA) and 5-HT, respectively, was observed in a large number of axons in the striae terminalis, the dorsal fornix, and the fimbriae hippocampi frontal to the lesion. These axons normally innervate the amygdala and the hippocampus, which were found to contain rather high levels of NA and 5-HT (Table) or between 5 and 15% of the total content of these amines in the entire brain. In those cases where the gyrus cinguli remained intact, an increased number of NA nerve terminals with an increased intensity were observed in this area. Retrograde cell body changes with inter alia a swollen appearance and a marked increased fluorescence intensity occurred in CA nerve cells in the ventro-lateral part of the reticular formation of the medulla oblongata (group A1 according to Dahlström and Fuxe 1964) (Figure 2). However, only part of the cell group (about 20%) was affected. Certain increases in fluorescence intensity were also observed in a small number of CA cell bodies of the pons whereas no certain increases could be seen in the mesencephalic CA

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cell groups. The number of cells with increased fluorescence intensity were highest after bilateral removal. After unilateral removal cells with increased fluorescence intensity were observed in group A1 mainly on the operated side but also on the unoperated side, indicating a certain degree of crossing. The 5-HT cell bodies and the NA and 5-HT nerve terminals of the lower brain stem all appeared unaffected.

Biochemically the cerebral cortex was found to contain rather high levels of NA and 5-HT (Table). Both the NA and 5-HT in the cortex were found to amount to about 25-30% of the total content of the amines in the entire brain.

Removal of the cerebellum. The cerebellum was usually completely removed with the exception of the lateral parts. The medulla oblongata and pons were usually not damaged. There was a marked increase in intensity in some of the CA cell bodies which appeared swollen and had a displaced nucleus. The changes were mainly limited to group A1 on both sides. The number of cells with retrograde changes was distinctly less than after removal of the cerebral cortex. A small number of CA cell bodies of the pons (mainly in the locus coeruleus area) showed similar changes. Otherwise no certain changes were observed in the fluorescence microscopical picture.

Biochemically, the normal rat cerebellum was found to contain a rather high concentration of NA but only a low one of 5-HT. This NA and 5-HT represented approximately 6–10 and 2–3%, respectively, of the total amount in the brain (Table).

The fact that there appear NA cell bodies with retrograde changes mainly in the medulla oblongata but also in the pons after removal of large parts of the cortex cerebri or the cerebellum indicate that most, if not all, of the NA nerve terminals in the cerebral cortex and in the cerebellum arise from axons which originate from NA cell bodies situated probably mainly in the reticular formation of the medulla oblongata (group A1) but also in the pons. In view of the present findings it may even be that the same NA neuron may innervate both the cerebral cortex and cerebellum, since the affected cell bodies lie in the same CA cell-group. A previous study[11] on the effect of large diencephalic-mesencephalic lesions on the monoamine neurons also support such a view, since increases in number and intensity of the NA nerve terminals were observed e.g. in the cerebellum and the medulla oblongata after such lesions. This is probably due to the fact that the amine storage granules which are produced in the cell bodies and transported down to the terminals via the axons[12,13], after such lesions are directed into the collaterals since the axons to the cerebral cortex and other forebrain structures had been damaged. The present findings of increases in the intensity and number of NA nerve terminals in the gyrus cinguli after removal of large parts of the cortex cerebri can be explained in the same way.

The present results also show that the NA and 5-HT axons innervating the cortex cerebri in all probability run in the cingulum, since a large number of non-terminal axons with high amounts of NA and 5-HT were found here after removal of parts of the cortex cerebri. Furthermore, after treatment with nialamide 5-HT axons ascending in the medial forebrain bundle have been seen to by-pass the septal area to enter the cingulum[14]. Studies on the uptake of CA and 5-HT after intraventricular injections have also revealed the presence of fibres able to accumulate NA and 5-HT in this area[15,16]. All these data taken together strongly support the present results. Fibre degeneration has also been observed with the method of Nauta and Gygax in the cingulum after lateral hypothalamic lesions[17,18].

Concentrations (μg/g; mean $\pm$ s.e.m.) of noradrenaline and 5-hydroxytryptamine in the cerebellum, the cerebral cortex, the amygdala and the hippocampus of normal rats. Number of determinations is indicated in parentheses.

	Noradrenaline	5-Hydroxytryptamine
Cerebellum	0.18 $\pm$ 0.010 (10)	0.07 $\pm$ 0.013 (4)
Cerebral cortex	0.25 $\pm$ 0.009 (8)	0.32 $\pm$ 0.020 (8)
Amygdala	0.37 $\pm$ 0.037 (6)	0.49 $\pm$ 0.068 (6)
Hippocampus	0.43 $\pm$ 0.041 (6)	0.32 $\pm$ 0.032 (6)

Zusammenfassung. In kombinierter histochemischer und biochemischer Untersuchung werden Dopamin-, Noradrenalin- und 5-Hydroxytryptamin-Neurone nach Entfernung von Cortex cerebri und Cerebellum studiert. Es ergibt sich, dass die Noradrenalin-Nerventerminale, welche Cortex cerebri und Cerebellum innervieren, vermutlich von feinen Axonen her stammen, deren Zellkörper mindestens zum Teil in der Formatio reticularis der Medulla oblongata gelegen sind. Die Noradrenalin- und 5-Hydroxytryptamin-Axone, die nach dem Cortex cerebri ziehen, passieren vermutlich zur Hauptsache das Cingulum.

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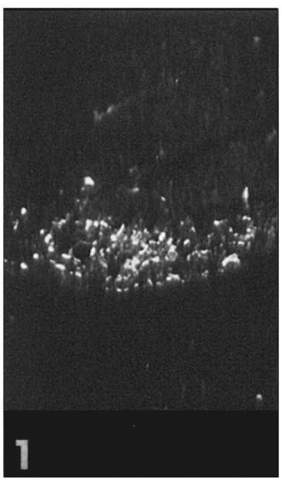
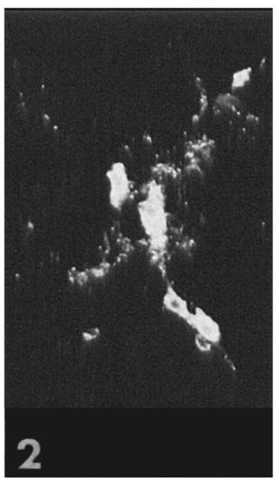
Department of Pharmacology, University of Göteborg and Department of Histology, Karolinska Institutet, Stockholm 60 (Sweden), 6th March 1967.





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Author Contribution Concept, writing, and approval of the final version: LCT and MM.

Funding Open access funding provided by HEAL-Link Greece

Declarations

Conflict of Interest The authors declare no competing interests.

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