The Cerebellar Serotoninergic System and its Possible Involvement in Cerebellar Ataxia

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ABSTRACT: A review concerning the characteristics of the cerebellar serotoninergic system is presented. In rat, cat and oppossum, the perikarya of origin are located in the brain stem raphe nuclei and in other brainstem structures. The projections to the cerebellar layers and deep nuclei include synaptic connections, but also non synaptic terminals, especially in a diffuse cortical plexus. Serotoninergic receptors have been described: 5-HT1B in the molecular layer and 5-HT2 in the inferior olive. Serotonin exerts neurophysiological effects on several target cells, directly or indirectly, presynaptically or postsynaptically. A modulatory effect on Purkinje cells is well documented. In thiamine deprived animals, a specific serotoninergic cerebellar syndrome includes a selective degeneration of the serotoninergic cerebellar system, an increase of the 5-HIAA cerebellar values and an exaggerated serotoninergic turnover. In human heredoataxias (Friedreich's ataxia and cerebellar cortical atrophy), serotoninergic disturbances have been observed in the CSF, including low 5-HIAA values and an increased serotoninergic turnover. Therapeutic results have been obtained with L-5-HTP, a precursor of serotonin, in several conditions presenting cerebellar ataxia. L-5-HTP resistance of olivo-pontocerebellar atrophies may be explained by the destruction of serotonin-sensitive target cells, especially Purkinje cells.

RÉSUMÉ: Le système sérotoninergique du cervelet et son implication possible dans l'ataxie cérébelleuse. Une revue décrivant les caractéristiques du système sérotoninergique cérébelleux est présenté chez le rat, le chat et l'oppossum, les neurones sont situés dans le tronc cérébral au niveau des noyaux du raphé mais aussi d'autres noyaux. Les projections aux différentes couches cérébelleuses et aux noyaux cérébelleux profonds comprennent des relations synaptiques, mais aussi des connections non synaptiques en particulier d'un plexus cortical diffus. Des récepteurs sérotoninergiques ont été décrits : 5-HT1B dans la couche moléculaire et 5-HT2 dans l'olive inférieure. La sérotonine exerce des effets neurophysiologiques complexes sur diverses cellules cibles directement ou indirectement, pré-synaptiquement ou post-synaptiquement. Un effet modulateur de la sérotonine sur les cellules de Purkinje est particulièrement documenté. Chez les animaux carencés en thiamine, une dégénérescence spécifique du système sérotoninergique cérébelleux est observé avec une exagération du "turnover" sérotoninergique. Dans les ataxies humaines – ataxie de Friedreich et atrophie cérébelleuse corticale – des anomalies sérotoninergiques comprenant en particulier une baisse du 5-HIAA dans le LCR et une élévation du "turnover" sérotoninergique ont été décrites. Des résultats thérapeutiques ont été obtenus avec le L-5-HTP, un précurseur de la sérotonine, dans divers sous-groupes de syndromes cérébelleux. La L-5-HTP résistance des atrophies olivo-ponto-cérébelleuses pourrait être expliquée par la destruction de ces cellules cibles dans ce groupe de maladies.

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Cerebellar ataxia is a complex disorder, involving several elementary motor control dysfunctions of trunk, limbs and phonation, as well as tonus abnormalities. Multiple defects in the neuronal circuitry, with specific electro-physiological abnormalities are likely to account for such a deficit. Yet, neurochemical hypotheses might also be proposed.

In 1980, we postulated that serotonin played a role in the production of human ataxia.[1,2] A large body of literature concerning monoaminergic terminals in the cerebellum existed, with some data on the involvement of the cerebellar serotoninergic system in experimental diseases including ataxia. We could show that a treatment with 5-HTP, a precursor of serotonin, was able to induce a partial regression of several aspects of cerebellar ataxia.[1-4]

The present review provides background information and details about the serotoninergic system and the serotoninergic hypothesis of cerebellar ataxia.

Anatomical Data: The Raphe Cerebello-Olivary System

In 1969, Hokfelt and Fuxe[5] described serotoninergic and noradrenergic afferent fibers to the cortex of adult rat cerebellum. Fuxe and Jonsson later mentioned[6] that the serotoninergic perikarya of origin might be located in the midbrain raphe nuclei B6 and B7. In cat, Shinnar et al.[7] demonstrated that horseradish peroxidase (HRP) injected in lobules VI and VII retrogradely labeled the rostral pole of nucleus raphe magnus, nucleus raphe pontis and raphe centralis superior. HRP injected in cat's flocculus retrogradely labeled nuclei raphe dorsalis and raphe centralis superior and inferior.[8] Batini et al.[9] showed that nucleus raphe pallidus was also related to lobule VII. Bobillier et al.[10] demonstrated that the raphe-cerebellar fibers emerged from the ventral border of nucleus centralis superior and reached the cerebellum via the brachium pontis. In the rat, Bishop and Ho[11] demonstrated that nucleus reticularis giganto-

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cellularis and nucleus reticularis para gigantocellularis also contained serotoninergic neurons projecting onto the cerebellum.

In the original work of Hokfelt and Fuxe in the rat,[5] the serotoninergic afferents were observed mainly in the molecular layer of the cerebellum, especially in the anterior lobe. The serotonin (5-HT) nerve terminals looked fine and varicose. They ran mainly in the transverse plan of the folium, parallel to the surface.

Chan-Palay[12-14] provided an extensive description of the cerebellar serotoninergic system, using light and electron microscopic autoradiography after intraventricular infusion of labeled 5-HT. In the cerebellar cortex, she observed a vast plexus of labeled indoleamine axons including 3 systems: (1) mossy-fiber-rosettes in the granular layer; (2) parallel fiber-like axons in the molecular layer; and (3) a diffuse branching plexus distributed to all layers. The deep cerebellar nuclei, dentate, interpositus and fastigius were also richly innervated.

Chan-Palay stressed the heterogeneity of connections of this system, which included classical synaptic contacts with dendrites of granule cells and cerebellar cortical interneurons, but also non-synaptic terminals probably delivering their neurotransmitter by neurohumoral dispersion.

The structural features of the raphe-cerebellar serotoninergic system were further investigated by Beaudet et Sotelo[15] and by Takeuchi et al.,[16] in the rat and cat. Bishop et al.[17] showed in the opposum that there was a distinct bundle of serotoninergic axons in the brachium conjontivum. In this species, the densest serotonin innervation was that of the Purkinje cell-granule cell border zone.

Purkinje cell dendrites are likely targets for the serotoninergic projections. However, according to Takeuchi et al.,[16] there was no morphological evidence that there are serotoninergic afferents terminating directly onto the somata of Purkinje cells.

Serotoninergic terminals are also present in the inferior olive, where they are particularly dense in the dorsal accessory and the medial accessory nuclei.[18-21] Remarkably, these serotoninergic terminals are mainly present in those olivary zones which receive direct spinal afferents[18,19] and project selectively onto the anterior lobe. This serotonin-regulated spino-olivary vermis system is likely to be involved in postural equilibrium functions.

The presence of cerebellar and olivary serotoninergic receptors has been suspected on the basis of neurophysiological[22,23] and anatomical studies.[12,13] Palacios et al.[24] were able to show, in the rat, significant densities of 5-HT1B and 5-HT1C receptors in the deep cerebellar nuclei, but low densities of sole 5-HT1B receptors in the molecular layer. High densities of 5-HT2 receptors were found in the inferior olivary nucleus.[24] In the mouse, strong hybridization signals of a recently cloned 5-HT1B receptor have been found present in the Purkinje cell layer.[25]

In man, the existence of the cerebellar serotoninergic system is highly probable, but has been difficult to demonstrate. Yet the existence of raphe serotoninergic neurons has been conclusively demonstrated (Chan-Palay et al.).[26]

Neurophysiological Data

From a physiological point of view, the Purkinje cell may be viewed as the major target cell of the cerebellar serotoninergic system. Bloom et al.[27] showed that the action of the monoamine was mainly inhibitory on Purkinje cells.

J.C. and H.K. Strahlendorf revealed diverse and complex effects of serotonin on Purkinje cells:[28-30] they were able to produce inhibition, excitation or biphasic responses. They discovered that the actions of serotonin are also dependent on the initial firing rate of the Purkinje cell: slow firing cells are accelerated while fast firing cells are slowed down. These authors postulated that serotonin may set the Purkinje cell to a preferred firing rate, thus acting as a stabilizing neuromodulator. Raphe stimulation induced an inhibition of Purkinje and fastigial cells, diminished by serotonin antagonists.[31]

Gardette et al.[32] reported that serotonin was also able to enhance the spontaneous firing of the cells of the deep cerebellar nuclei. However, when studying the excitatory responses of Purkinje cells and deep cerebellar nuclei neurons to the excitatory aminoacids (glutamate and aspartate), Gardette and Crepel[33] showed that serotonin was able to decrease these responses. This effect being maintained in the presence of TTX and in low-calcium medium, a post-synaptic site of action was probable. Since this effect also occurred at doses at which there was no direct effect on Purkinje cells, it is suggested that the implicated receptors were different from those of the direct inhibition.

Raiteri et al.[34] showed that the endogenous release of glutamate by rat cerebellar slices was potently inhibited by the stimulation of both 5-HT_1A-like and 5-HT2 receptors. The 5-HT_1A-like receptors appear to be sited on glutamatergic terminals originating from climbing and parallel fibers, while the 5-HT2 receptors would be on "giant" mossy fiber terminals.[35] Thus, serotoninergic afferents seem to exert a powerful physiological control on the postsynaptic effects of glutamatergic cerebellar afferents.

Serotoninergic manipulations *in vivo* have been shown to deeply disturb cerebellar functions. Thus, harmaline, an indolic MAOI-A having a structural analogy with 5-HT, is known to suppress the firing activity of dorsal raphe neurons, while enhancing the discharge rate of cortical cerebellar neurons and synchronizing that of inferior olivary neurons (Weiss and Pellet).[36]

Therefore, serotonin seems to have not only direct modulatory effects on Purkinje cells, deep cellular nuclei neurons and olivary cells, but also multiple indirect modulatory effects on the presynaptic delivery of glutamate and the post-synaptic action of glutamate.

Ataxia and Serotoninergic Impairment in Experimental Models

Thiamine Deprivation

In 1977, Chan-Palay, Plaitakis, Nicklas and Berl[37] described autoradiographically a loss of labeled serotoninergic axons in the cerebellum of thiamine-deprived rats, affecting the mossy fiber system and the parallel fiber-like neurons. Serotoninergic terminals in the inferior olive were also affected.

The selectivity of the biochemical impairment of the cerebellar serotoninergic system was underlined by Plaitakis et al.,[38,39] who were able to show a decrease of serotoninergic synaptosomal uptake in affected animals. This abnormality was correlated with the development of ataxia. Plaitakis et al. later demonstrated

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that serotoninergic abnormalities also included an exaggeration of the cerebellar serotonin turnover and an increase of cerebellar 5 HIAA values.[40]

On this experimental basis, a possible relationship between ataxia and cerebellar serotoninergic disturbances has been postulated by Chan-Palay[37] and Plaitakis et al.[39]

Of course, selective reductions of serotonin uptake might be due to primary midbrain lesions. Kuhar et al.[41] had indeed shown in 1972 that midbrain raphe lesions were able to induce a selective reduction of serotonin synaptosomal uptake in rat forebrain.

Genetic Models

Ghetti et al.[42] using pcd mutant mice, showed a decrease of the serotonin turnover and low 5-HIAA values in late stages of the disease. Experiments with probenecid indicated that this reduction of the serotonin turnover was restricted to the cerebellum.

In the "reeler mouse", Oshugi et al.[43] showed that tryptophan hydroxylase was significantly reduced in the brain stem, while 5-HIAA and serotonin values were markedly increased in the cerebellum.

Human Biochemical Studies

Heredoataxias

While a reduction of the cerebellar noradrenaline values in OPCA patients has been described, there have been no measurements of cerebellar serotonin and 5-HIAA content in patients having suffered of heredoataxias. There have been no reports of serotonin abnormalities in the CSF of patients with Friedreich ataxia or cerebellar atrophies.[44]

In the CSF of Friedriech ataxia and cerebellar atrophy patients, we found[45] low baseline values of 5-HIAA. With the probenecid test, we were able to show that there is a significant increase of the serotonin turnover. This neurochemical syndrome might be due to an increased efflux of 5-HIAA and an increased turnover of serotonin.

However, these impairments do not appear to be selective, since we could observe significant HVA variations in the same direction as those of 5-HIAA.

Primary Serotonin Metabolism Abnormalities and Ataxia

In 1956, Baron et al.[46] described a hereditary disease characterized by fluctuating cerebellar ataxia associated with abnormal tryptophan metabolism.

In 1959, Southren et al.[47] published in 1959 the case of a 49-year-old woman with hyperserotoninemia and a clinical syndrome including hypertension, flushes and ataxia. 5-HIAA values were normal in urine indicating an abnormal pathway in metabolizing endogenous serotonin. A functional deficiency of brain-tissue serotonin was hypothesized. Improvement in ataxia by diphenyl hydantoïn was observed together with the normalization of serotoninemia. Reserpine provided an aggravation of the ataxia and mental disturbances.

Pharmacological Data

In 1977, we treated a first case of cerebellar ataxia due to a carential regimen with a daily dose of 500 mg of DL-5-HTP. A film was made showing a partial regression of static ataxia. Particularly striking was the diminishing of the anteroposterior rapid sway over the next two weeks.

Twenty-six patients were then gathered, suffering from Friedriech ataxia, late cerebellar cortical atrophy, olivo-ponto cerebellar atrophy and post surgical injuries. In 1980,[1-4] following accurate quantitative evaluation, we were able to show that DL-5-HTP at the dose of 16 mg/kg/day was partially active on cerebellar ataxia of specific conditions. Friedreich ataxia was often sensitive at the beginning of its evolution, but the degenerative process continued. Several cases of cortical cerebellar atrophies were responders. Yet, even in these hereditary sensitive conditions, only 6 out of 19 patients were statistically significant responders. OPCAs appeared resistant. The levotoratory form of 5-HTP was shown to be more active than the racemic form, in sensitive conditions. Its effect was particularly noticeable on the static components of the ataxias and on speech. Kinetic performances were less consistently improved. A considerable increase of the CSF serotonin turnover was demonstrated in treated patients.[4]

We confirmed, with a double blind study carried out on 30 patients, that levotoratory 5-HTP was the biologically active form of the molecule.[48] The beneficial effects in cases of cerebellar atrophies were confirmed. Again, static and speech performances were found to be more sensitive than static symptoms.

The response of cerebellar ataxia to 5-HTP was confirmed by Rascol et al.,[49] Wessel et al.[50,51] and Mertens and Kohlepp.[52] Again, it appeared that only half of the patients were sensitive.

The qualitative evaluation of the therapeutic effects underlines the sensitivity or resistance of the ataxias depending on their etiology. L-5-HTP sensitivity and L-5-HTP resistance are observed in hereditary and acquired ataxias.[53] The hereditary dominant forms of cerebellar atrophies are consistently sensitive. Conversely, most cases of OPCA can be considered as resistant, in our experience. Machado-Joseph disease is definitely resistant. Friedreich's ataxia may be sensitive at the beginning of its evolution, when standing is still possible. In cases with more severe symptoms, the return of the balance capacities in the sitting position may be observed, while the other components of ataxia do not appear to be clearly influenced. Ataxia in multiple sclerosis, when the disease is stabilized by an azathropine regimen, is often sensitive. Post-infectious ataxias with heavy cortical cerebellar destruction are resistant. Patients with lacunes in the brain stem may have rapid responses to L-5-HTP (Trouillas, 1993).[54] In these cases, we hypothesize lesions interrupting the raphé-cerebellar serotoninergic bundles, thus inducing a cerebellar "serotoninergic disconnexion". The integrity of Purkinje cells might account for the good effect induced by the molecular replacement in these patients.

Adequate dosage and the utilization of a decarboxylase inhibitor are useful for obtaining significant results in routine therapy. Intolerance has been observed, manifested by diarrhea, nausea, vomiting, and sleepiness. Gastrointestinal symptoms are minimized by the administration of a decarboxylase inhibitor. The standard dose of L-5-HTP is 10 mg/kg/day. High doses may be needed in cerebellar atrophies: a dose of 16 mg/kg/day with a decarboxylase inhibitor has been administered for years. To reach such a level safely, the increase in L-5-HTP and inhibitor dosage should be progressive. Benserazide should not be used before the age of 22 because of metaphysal growth disturbances.

Conclusions

The neuropharmacology of cerebellar ataxia includes few molecules: propanolol, physostigmine, choline and TRH. None have shown a clear-cut benefit. The manipulation of serotonin, on the basis of a possible impairment of the serotoninergic cerebellar system in ataxia, has led to an imperfect, but interesting therapy, in some cases of cerebellar ataxia.

These data also call for a reconsideration of the understanding of cerebellar ataxia itself. In the mechanism of the syndrome, conventional deficits of myelinated fibers and/or of ongoing effector devices might not be the sole origin of this cerebellar dysfunction. An important part of ataxia might be due to long term neurotransmitter deficits resulting from anatomical "monoaminergic disconnexions" (multiple sclerosis, lacunes) or from alterations of the neurotransmitter metabolism, primary or secondary. Serotonin might be one of these transmitters. Thus, the replacement of serotonin, especially when the Purkinje cells are intact, might account for the therapeutic effects of L-5-HTP. Conversely, destruction of target cells by severe degenerative processes would thus account for L-5-HTP resistance.

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