Modulation of Monoaminergic and Amino Acid Transmission as a Means for Therapeutic Intervention in Ataxia

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ABSTRACT: In recent years, substantial progress has been made in understanding the organization and function of the cerebellum at the neuronal, synaptic, and molecular level. More than any other region of the brain, the cerebellum utilizes amino acids as its main excitatory and inhibitory transmitters. Excitatory amino acids, such as glutamate and aspartate, in addition to serving as chemical messengers, may also mediate neurodegenerative processes in human ataxic disorders. Of the monoamines, serotonin has been proposed as a neuromodulator in the cerebellum and is thought to play a role in the pathophysiology of ataxia in animal models, and human cerebellar disorders. These considerations raise the possibility that pharmacologic modification of amino acid and serotonergic transmission may provide a means for therapeutic intervention in ataxia.

RESUME: Modulation de la transmission monoaminergique et aminoacidergique comme moyen therapeutique dans l'ataxie. Des progres substantiels ont été réalisés dernièrement dans la comprehension de l'organisation et de la fonction du cervelet au niveau neuronal, synaptique et moleculaire. Plus que dans toute autre region du cerveau, le cervelet utilise des acides amines comme neurotransmetteurs excitateurs et inhibiteurs principaux. Les acides aminés excitateurs tels que le glutamate et l'aspartate, en plus de servir de messagers chimiques, peuvent aussi medier des processus neurodegeneratifs dans les desordres de type ataxique chez l'humain. Parmi les monoamines, la sérotonine a été proposee comme un neuromodulateur dans le cervelet et on lui attribue un rôle dans la pathophysiologie de l'ataxie dans les modeles animaux et dans les affections cerebelleuses chez l'humain. Ces considerations soulèvent la possibilité que des modifications pharmacologiques de la neurotransmission par les acides aminés et la sérotonine puissent fournir un moyen d'intervention therapeutique dans l'ataxie.


Ever since the success of neurotransmitter replacement therapy for Parkinson's disease (PD), there has been hope that similar approaches, using modulation of chemical transmission, might be developed for other human neurodegenerative disorders, including the cerebellar ataxias. To this date, however, such expectations have not materialized. The reasons for this appear to be multifold.

In typical PD there is a rather selective degeneration of the nigrostriatal pathway. Despite this loss of pre-synaptic terminals, striatal post-synaptic neurons bearing dopaminergic receptors are essentially preserved. In untreated PD patients, striatal dopamine receptors may even be increased (denervation hypersensitivity). PD, in its typical dopamine-sensitive form, is quite homogeneous. A positive therapeutic response to dopaminergic agents has been one of the criteria used to separate primary PD from secondary forms of the disease (symptomatic parkinsonism) which are often refractory to such treatment. Unlike typical PD, the cerebellar ataxias are clearly heterogeneous. The histopathologic changes that occur in most of these disorders are rather diffuse with post-synaptic receptors being markedly reduced. Transynaptic degeneration, shown to occur in cerebellar mutant animals, may be responsible for the development of these changes.

Much of the chemical transmission in the basal ganglia is mediated by certain biogenic amines whereas, in the cerebellum and spinal cord, such monoaminergic systems appear to play a lesser role in neurotransmission processes. The monoaminergic neurons have been well characterized with respect to the factors that regulate the synthesis, catabolism, storage, release, and termination of action of their transmitters. Thus, it has been possible to develop a variety of therapeutic approaches which are based primarily on the modulation of different aspects of neurotransmission.

Neurotransmission in the cerebellum seems to be mediated primarily by excitatory and inhibitory amino acids. Unlike the monoaminergic neuromodulators, some of these amino acid transmitters (particularly those with neuroexcitatory function) are present in all cells serving multiple functions, including metabolic processes. Although distinct pools have been identified to serve these diverse needs, these pools appear to remain in

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equilibrium. As such, it has been difficult to selectively modulate a particular neurotransmitter function without causing more generalized alterations. The factors regulating the synthesis, storage, release and catabolism of amino acid transmitters have not been as well understood as those governing the monoamine transmitters. In addition, post-synaptic transduction by amino acid transmitters has proven to be quite complex. Multiple glutamate receptors have been shown to exist exhibiting ligand specificity and differences in signal processing, desensitization and other features.

Given these considerations, it is not surprising that pharmacological therapies, tried in ataxia, have not been particularly successful. Nevertheless, certain promising approaches, based on modulation of serotonin, GABA and glutamate-mediated transmission, have emerged in recent years.

**Modulation of Serotonergic Transmission**

Although the serotonergic innervation of the cerebellum is not as dense as in other brain regions, there are at least two lines of evidence that serotonergic transmission may be important in cerebellar function. The first is provided by studies on an animal model of ataxia induced by thiamine deficiency which revealed abnormalities in the cerebellar serotonergic system, and the second by the positive therapeutic effects observed in ataxic patients treated with serotonin precursors.

In experimental thiamine deficiency induced chronically by diet or acutely by the use of thiamine antimetabolites, the high affinity serotonin uptake by cerebellar synaptosomes was significantly decreased. This was associated with increased regional brain levels of 5-hydroxyindolacetic acid (5-HIAA) resulting from an enhanced brain serotonin turnover in these regions. The greatest changes observed were in the cerebellum. In addition, morphological changes involving brain serotonergic neurons have been detected by autoradiography.

Recently, glutamatergic excitotoxic mechanisms have been suggested in the pathogenesis of thiamine deficiency encephalopathy. Moreover, neuroexcitotoxic compounds can induce biochemical and morphological alterations affecting serotonergic neurons which are similar to those observed in thiamine deficiency. Because the content of serotonin in the brains of animals exposed to neuroexcitotoxic agents, as in thiamine deficiency, were not altered, damage to serotonergic neurons was considered to be unlikely. However, it is possible that this may occur in chronic thiamine deficiency. In view of these experimental data, it is of particular interest that 5-HIAA concentrations have been recently shown to be increased in the striatum of patients with olivopontocerebellar atrophy.

Based on these observations, Trouillas et al. evaluated the possible therapeutic effects of the serotonin precursor L-5-hydroxytryptophan (L-5-HTP) in ataxia. They observed beneficial effects in some patients with cerebellar cortical degeneration or cerebello-olivary atrophy (disorders characterized by predominant midline cerebellar dysfunction), as well as in ataxic patients with brain stem lesions. Interestingly, static and speech performances were found to be more responsive to L-5-HTP treatment than other symptoms and signs of cerebellar dysfunction. Hence, the deficits sensitive to L-5-HTP treatment, as with those produced by thiamine deficiency, appear to arise from midline cerebellar dysfunction.

About 10 years ago we had the opportunity of studying a 33-year-old female patient with persistent neurological deficits resulting from a bout of acute thiamine deficiency encephalopathy. This developed after gastric partitioning for morbid obesity complicated by persistent vomiting. Following thiamine treatment of the acute encephalopathy, she was left with disabling neurologic symptoms. A year after her acute encephalopathy, the patient complained of severe oscillospia, rolling vision, and a visual illusion of environmental movement on head rotation. Objectively, there was gaze-evoked horizontal nystagmus as well as vertical nystagmus of variable intensity which was often present with gaze in the primary position. She also showed dysarthria, intention tremor, slight appendicular dystaxia and a greater degree of gait ataxia. Her symptoms were markedly aggravated by position changing and by head movements making ambulation problematic.

Following initiation of therapy with L-5-HTP and the peripheral aromatic amino acid decarboxylase inhibitor carbidopa, and after the dosage level of L-5-HTP reached 400 mg/daily, the patient experienced improvement in her ability to read and to turn her head without experiencing a sense of environmental rotation. Her stance improved and her oscillospia and tremor diminished. Other cerebellar deficits showed little change. These improvements have been maintained for over 10 years while the patient has remained on L-5-HTP therapy (600 - 1,200 mg/daily). Although, it is difficult to generalize on the basis of a study of a single case, these observations provide additional evidence that L-5-HTP therapy can modify aspects of cerebellar dysfunction, particularly those resulting from midline involvement.

Along these lines of thought, the recent characterization of different subtypes of serotonin receptors and the development of drugs capable of interacting specifically with these receptors, have opened new avenues for therapeutic intervention in ataxia. Unlike the serotonin precursor L-5-HTP which is expected to act on multiple serotonin receptors thus eliciting complex responses, some of the recently developed drugs can interact quite specifically with one subtype of serotonin receptors. Therefore, these agents are capable of modulating particular aspects of serotonergic transmission. Recently, it has been shown that serotonin acting on 5-HT and 5-HT types of receptors can regulate the release of the major excitatory amino acid glutamate. There is even evidence that the 1B subtype of 5-HT receptor is capable of modulating presynaptic autoreceptors which regulate the release of GABA, the major inhibitory amino acid transmitter utilized by cerebellar systems.

**Modulation of GABAergic Transmission**

GABA is a major inhibitory neurotransmitter utilized by the Purkinje cells, the principal neurons of the molecular layer that often degenerate in the various ataxias. Also, the dentate cerebellar output system is thought to utilize GABA as its neuromodulator. It would be logically expected, therefore, that enhancement of GABAergic transmission could provide a means for therapeutic intervention in ataxia. Clinical experience, however, has not so far substantiated these expectations. The same also holds true for the treatment of chorea, a movement disorder that has been linked to GABAergic deficiency in the striatum. Various attempts have been made using agents that...
1) interact directly with post-synaptic receptors (GABA agonists), 2) inhibit the uptake of GABA or 3) alter the synthesis or degradation of this amino acid. With respect to the latter, there are reports that isoniazid, a GABA transaminase inhibitor, used together with pyridoxine, can alleviate cerebellar tremor.\textsuperscript{14} It seems, however, that this effect is mild and, more important, this treatment does not modify other disabling aspects of cerebellar dysfunction occurring in ataxia patients.

In addition, there are reports that clonazepam, an agent that may interact with the brain GABAergic system, can provide some symptomatic relief to ataxia patients.\textsuperscript{15} We have found that small doses of this medication (0.5 mg - 3 daily) may improve handwriting and alleviate tremor or even head titubation in some ataxia patients, particularly in those with prominent tremor. Paradoxically, higher doses of this medication are known to aggravate ataxia as do other benzodiazepines and anti-convulsants thought to interact with brain GABAergic mechanisms. The complexity of the GABAergic receptors, already shown to be differentially altered in cerebellar degenerations,\textsuperscript{2} may play a role in these seemingly conflicting effects. Further studies are needed to better understand the role of the GABAergic system in cerebellar physiology and pathophysiology as a prerequisite for developing therapeutic approaches that are based on the modulation of this system.

**Modulation of Excitatory Transmission**

Much of the experimental evidence suggests that the excitatory amino acids, glutamate and aspartate, play a major role in cerebellar function. Glutamate has been specifically suggested as the excitatory transmitter of the mossy fiber afferents and the cerebellar granule cells that project to the Purkinje cells. Aspartate may serve as the excitatory transmitter of the olivo-cerebellar fiber afferents which also synapse with the Purkinje cells. Cerebellar disorders that are characterized by degeneration of these systems, such as the cerebello-olivary and olivoponto-cerebellar atrophies, are therefore expected to be associated with a decreased excitatory afferent input to the cerebellar cortex.

Another important issue that relates to neuroexcitatory amino acids, is their ability to cause neuronal degeneration under conditions of enhanced excitation (neuroexcitotoxic hypothesis).\textsuperscript{16} This may be an important pathogenetic mechanism for cerebellar disorders that are associated with altered metabolism of these compounds. Deficiency of glutamate dehydrogenase (GDH) is one of the metabolic defects thought to lead to excessive accumulation of glutamate at the synaptic cleft with resultant degeneration of the post-synaptic neurons.\textsuperscript{17} However, glutamate levels have been found to be decreased in the cerebellar tissue of patients who came to autopsy.\textsuperscript{18} These findings have been explained as resulting from an altered distribution of nervous tissue glutamate with intracellular levels being decreased while extracellular (synaptic) concentrations are elevated. The finding that post-synaptic glutamate receptors are decreased in cerebellar tissues from such patients\textsuperscript{12} is consistent with this possibility.

Although this neuroexcitotoxic hypothesis for cerebellar degenerations is in accord with that proposed for other human degenerations,\textsuperscript{16} there are intriguing observations\textsuperscript{19,20} indicating that glutamate receptors, such as the NMDA receptors, which have been linked primarily with neurotoxic phenomena, may also play a trophic role in developing cultured cerebellar neurons. These observations, taken together with the above data showing decreased glutamate levels in cerebellar tissue of ataxia patients, raise further questions related to the pathogenesis of these neurodegenerations. Hence, is not entirely clear, at present, whether modulation of glutamatergic transmission should be toward enhancing or blocking glutamatergic transmission.

Therapeutic interventions aimed at attenuating glutamatergic transmission can be directed toward: 1) decreasing the release of glutamate, 2) enhancing its metabolism and/or 3) blocking its post-synaptic receptors. Lioresal is one of the drugs that can decrease glutamate release but there is no present indication that this medicine can modify ataxia or the course of cerebellar degenerations. As indicated above, a new class of medications has recently become available which is capable of influencing presynaptic glutamate release by interacting with serotonin receptors.\textsuperscript{12} Hence, these agents provide an alternative approach for modulating glutamatergic transmission in ataxia patients.

Blocking the post-synaptic glutamate receptors as a means for therapeutic intervention in human degenerative disorders has received much publicity with most attention being focused on drugs which interact with the NMDA receptor.\textsuperscript{16} In the cerebellum, however, excitatory transmission is mediated primarily by the non-NMDA glutamate receptors.\textsuperscript{2} Another concern is that attenuating excitatory transmission, thought to be decreased in cerebellar disorders, could aggravate cerebellar dysfunction. However, this approach may lead to a longterm benefit by attenuating glutamate-induced neuroexcitotoxicity. It is of interest that therapeutic benefits have been described by Botez et al,\textsuperscript{21} in OPCA patients treated with amantadine HCl, an agent capable of blocking glutamate receptors. Hence, this is a promising avenue that needs further evaluation.

In recent years, the branched chain amino acids L-leucine, L-isoleucine and L-valine, compounds capable of stimulating GDH activity, have been used for the treatment of GDH-deficient OPCA\textsuperscript{22} and other degenerations associated with altered glutamate metabolism.\textsuperscript{23} GDH is enriched in CNS regions that receive glutamatergic innervation, where it is localized in glial processes associated with glutamatergic nerve terminals and is thought to play a major role in the oxidation of transmitter glutamate by these cells.\textsuperscript{23} Stimulation of GDH activity is therefore expected to enhance synaptic glutamate detoxification and thus halt or retard the neurodegenerative process.\textsuperscript{23,24} We have, thus far, treated several OPCA patients with or without GDH deficiency using either a combination of pure branched-chain amino acids\textsuperscript{22} or a commercial diet rich in these substances.\textsuperscript{24} Although we have observed no reversal of existing neurologic deficits, some patients with partial GDH deficiency have shown little progression or even stabilization of their disease while on the dietary supplementation for up to 10 years. In contrast, patients with a form of OPCA that is associated with progressive autonomic failure (non-GDH deficient) did not appear to derive any benefit from such treatment. The rarity with which these disorders are encountered has not permitted us to conduct a randomized controlled study. It is therefore difficult to draw definite conclusions on the basis of these limited observations.

Although a successful treatment of ataxia has not yet materialized, there are reasonable hopes that this can be achieved in the near future. For reasons detailed in this report, therapeutic approaches aiming at modification of glutamatergic,
GABAergic and serotonergic transmission are promising and, therefore, need to be vigorously pursued.

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