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Understanding Essential Tremor: Progress on the Biological Front

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Abstract

For many years, little was written about the underlying biology of ET, despite its high prevalence. Discussions of disease mechanisms were dominated by a focus on tremor physiology. The traditional model of ET, the olivary model, was proposed in the 1970s. The model suffers from several critical problems and its relevance to ET has been questioned. Recent mechanistic research has focused on the cerebellum. Clinical and neuroimaging studies strongly implicate the importance of this brain region in ET. Recent mechanistic research has been grounded more in tissue-based changes (i.e., postmortem studies of the brain). These studies have collectively and systematically identified a sizable number of changes in the ET cerebellum, and have led to a new model of ET, referred to as the cerebellar degenerative model. Hence, there is a renewed interest in the science behind the biology of ET. How the new understanding of ET will translate into treatment changes is an open question.

Keywords

essential tremor; biology; pathophysiology; cerebellum

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Elan D. Louis declares that he has no conflict of interest.

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Introduction to ET

Essential tremor (ET) stands out as one of the most prevalent neurological diseases.[1, 2] Its most recognizable clinical feature is an 8–12 Hz action tremor (i.e., a tremor that occurs during volitional movement) of the arms; head tremor and other cranial tremors may also occur,[3, 4] as well as limb and gait ataxia and subtle eye motion abnormalities.[5–7] The disease is progressive,[8, 9] and the tremor is often disabling.[10, 11] The one prospective population-based study of ET mortality indicated a modest (45%) increased risk in ET cases.[12]

ET is the most common tremor disorder. The disease is present in 4.0% of individuals aged ≥40,[1] and the incidence[13] and prevalence[1] increase with age, so that as many as 22%–23% of persons aged >90 years have ET.[14] The condition is clearly global, affecting humans of all ethnicities, from the remote Okapa sub-district of Papua New Guinea to the urban community of Washington Heights-Inwood in northern Manhattan, New York.[14, 15]

The underlying causes of ET are far from fully elaborated, although genetic and environmental factors are both likely to play a role. Recent studies have identified several genetic candidates;[16, 17] however, the study of ET genetics remains in its infancy.[18] There are several interesting leads in terms of environmental risk factors,[19] some of which could be modifiable exposures (e.g., harmane and ethanol).[20, 21] Evidence of etiological, clinical, pathological and pharmacological response phenotypical heterogeneity have led to the notion that the entity “ET” may indeed represent a family of diseases better encapsulated by the term “the essential tremors”.[22, 23]

The Biology of ET – Where are we Coming From?

For many years, little if anything was written about the underlying biology of ET, despite the high prevalence of the disease. Curiously, many textbook chapters and review articles on ET did not include a section devoted to disease pathophysiology.[24] This paralleled the notion that ET was not really a disease per se, but rather, a relatively benign constitutional trait; as such, the loose terms “disorder” and “condition” were often applied to ET rather than the more definitive term “disease”.[24] A PubMed search conducted in June 2013, crossing the terms “essential tremor” and “biology”, yielded only 17 entries, none of which included the term “biology” in the article title,[25] and a recent review of the 100 most cited papers on ET revealed that none dealt with issues related to molecular or cellular biology.[26]

The Biology of ET – Older Disease Models

Discussions of disease mechanisms in ET, although sparse, were for many years dominated by a focus on tremor physiology and brain circuitry.[27, 28] The existence of a central tremor pacemaker or oscillator was posited; the main support for this idea was the existence of an animal model of action tremor using the neurotoxin harmaline (similar to harmine and harmane), which induces a non-specific action tremor in laboratory animals and postmortem changes in the olivocerebellar pathway in these animals.[24, 29, 30] Buoyed by this observation, a physiological derangement in the inferior olivary nucleus, a structure which has inherent oscillatory-pacemaking properties, was viewed as the possible prime mover in

ET,[28] although there was very little actual empiric support for what was more of a theoretical physiological construct.[24, 25]

As noted above, the traditional model of ET, the olivary model, was first proposed in the early 1970s.[25, 29, 31] The olivary model is based on three primary observations. First, the β-carboline alkaloids (e.g., harmaline, harmine, harmane, and several other related molecules), are a class of chemicals that are highly neurotoxic, and their administration to a broad range of laboratory species produces action tremor, which is the hallmark feature of ET.[32, 33] These toxins, by producing excessive climbing fiber-derived glutamate discharge, result in marked Purkinje cell destruction.[34] Second, a variety of neurons in the central nervous system have pacemaking properties, that is, they are capable of firing in a coordinated and rhythmical fashion.[31] Among the many neurons with pacemaking properties are the climbing fibers whose cell bodies are situated in the inferior olivary nucleus.[30, 35, 36] Third, early studies on the pathology of ET incorrectly concluded that there was no ET pathology.[37] These studies, however, were based on exceedingly small numbers of ET cases, a limited examination of the cerebellum, lack of a quantitative approach to assess morphological changes, and an absence of control brains for comparison.[25, 31, 37]

The olivary model is based on sound primary neurophysiological observations, yet as reviewed in detail elsewhere,[25] there are major problems with the model (Table 1). First, there is no empirical evidence that the hypothesized process is occurring in the human disease ET.[31] In other words, the model is purely conjectural.[25] Second, pacemakers exist in numerous locations in the central nervous system, including the locus ceruleus,[38] dorsal raphe nucleus,[39] thalamus,[40] and the cerebellum (Purkinje cells) itself.[41] Thus, olivary pacemakers are not unique, and there has been no attempt to explain why these rather than the numerous other pacemakers are posited to be patho-mechanistically relevant in ET.[25, 31] Third, the harmaline model is an animal toxin model of tremor rather than a model of the human disease, ET, which occurs in nature. Action tremor is a non-specific neurological sign, and is not the equivalent of the human disease ET.[31] Also, harmaline-exposed animals develop an acute tremor that resolves after a few hours. Hence, it is a model of acute action tremor rather than chronic action tremor.[25, 31] Finally, positron emission tomography studies over the past two decades, have not demonstrated involvement of the inferior olivary nucleus in ET, nor have later postmortem studies revealed structural changes in that nucleus.[42, 43] In summary, the olivary model of ET suffers from a number of critical problems.[25, 31] Its relevance to ET has been called into question.[31]

As a result of growing awareness of problems with the olivary model, and the emergence of new science focused on the biology of ET (as discussed below), the olivary model is falling out of favor.

A New Biology of ET – Zeroing in on the Cerebellum

In recent years, mechanistic research on ET has focused more on the cerebellum and the role it plays in the biology of this disorder. Interest in the cerebellum was initially motivated by clinical and neuroimaging studies, which strongly implicate the importance of this brain region in ET.

An emerging clinical literature has gathered increasing support for the notion that the cerebellum itself might be centrally involved in ET. First, cerebellar-like problems, with abnormalities in tandem gait and balance, have been repeatedly described in ET patients.[24, 44–47] Intention (i.e., "cerebellar") tremor of the arms occurs in approximately one-half of ET patients,[48] and in 10% of ET patients, intention tremor involves the head as well.[24, 49] There are a variety of other motor abnormalities that point to what is likely to be a more pervasive underlying abnormality of cerebellar function in ET. These include oculomotor deficits[5] as well as abnormalities in limb motor behavior in ET.[24, 50–53] Second, unilateral cerebellar stroke has been reported to abruptly terminate ipsilateral arm tremor in patients with ET.[54, 55] Third, cerebellar outflow (dentato-rubro-thalamic) pathways are the target(s) of deep brain stimulation, which is a therapy that is highly effective in treating ET.[24, 56, 57]

A wide array of neuroimaging methods used in an ever-growing number of studies now indicate the presence functional, metabolic and structural abnormalities in both the cerebellar gray and white matter.[58] These studies include functional magnetic resonance imaging (MRI) studies,[59] positron emission tomography studies,[42, 60, 61] [^{1}H] magnetic resonance spectroscopic imaging studies,[62, 63] diffusion tensor imaging studies,[64–66] voxel based morphometry studies,[67, 68] and studies using other automated volumetric methods.[69]

A New Biology of ET – The Rise of Tissue-Based Studies

Mechanistic research on ET in recent years has been grounded more in empiric, controlled, tissue-based changes (i.e., postmortem studies of the brain). Postmortem studies in recent years have systematically identified a sizable number of changes in the ET brain, across each of the following cerebellar compartments (Table 2): (1) Purkinje cell dendrites (i.e., an increase in number of Purkinje cell dendritic swellings),[70] (2) Purkinje cell body (i.e., both reductions in Purkinje cell linear density as well as heterotopic placement of Purkinje cell soma),[71–73] (3) Purkinje cell axon (i.e., a broad range of changes in axonal morphology, including torpedoes),[3, 72] and (4) basket cell axonal processes (i.e., hypertrophy of perisomal processes ["hairy baskets"] and elongated LINGO1 labeled pinceau processes).[74, 75] Systematic postmortem study of the other brain regions that form loop connections with the cerebellum (i.e., the thalamus, inferior olivary nucleus, red nucleus, and motor cortex) indicate that significant pathologic changes are not evident in these brain regions,[76, 77] reinforcing the notion that the cerebellum is the focal point of interest in studies of the pathogenesis of ET.

A New Biology of ET – The Cerebellar Degenerative Model

The recent tissue-based research has led to a new model of ET, namely, the cerebellar degenerative model. The model is not new and, in fact, the idea that ET could be neurodegenerative was proposed more than 50 years ago.[78] Now, however, there is accumulating empiric support for this notion. This model posits that ET begins with an as-yet unidentified molecular event that stresses the Purkinje cell population, and this stress is evidenced by structural changes in that population.[79] One of the most obvious changes in the ET cerebellum is an increase in the number of torpedoes. These are abnormal ovoid

swellings of the proximal portion of the Purkinje cell axon, and there is an approximately seven-fold increase in these structures in ET brains compared with age-matched control brains,[37, 72] with detailed assessments showing that a single Purkinje cell axon in ET may contain several (i.e., two or three) such torpedoes.[24, 79] Torpedoes, which contain a massive accumulation of abnormally phosphorylated and disorganized neurofilaments,[80–82] and these neurofilament mis-accumulations are thought to inhibit both anterograde and retrograde axonal transport, ultimately leading to cell strangulation.[79, 83–85]

This axonal strangulation likely leads to regenerative behaviors, with attempts at axonal remodeling. In general, the Purkinje cell response to stress/disease involves a range of axonal changes.[86] Thus, Purkinje cells, in contrast to most neurons in the central nervous system, often still survive despite marked injury,[86–88] and they may exhibit a vigorous inclination towards sprouting and other changes both along the intracortical segment and the distal stump.[89–92] More specifically, the axonal changes that occur to a significantly greater extent in ET than control brains include: an increased number of arciform axons (i.e., axons that gradually curve back towards the Purkinje cell layer rather than continuing downward to the deep cerebellar nuclei – i.e., axons that seem to be heading in a cortical direction rather than a cortico-fugal direction), the formation of axon recurrent collaterals (i.e., axons or axon branches that make at least a 90° turn back towards the Purkinje cell layer), increased axonal branching (i.e., the presence of axons with at least one branch point and as many as multiple bifurcations), and increased terminal axonal sprouting (i.e., the presence of a frayed terminal axonal region juxtaposed within or near to the Purkinje cell layer).[79, 93] These structural abnormalities indicate a likely increase in aberrant Purkinje-Purkinje interactions and/or aberrant Purkinje cell interactions with other neurons.

In the cerebellar degenerative model of ET, it is posited that the stress to the Purkinje cell and/or torpedo-associated axonal strangulation leads to the selective degeneration and, in some instances, death of Purkinje cells.[79, 94–98] Of interest is that the reduction in numbers of Purkinje cells is greatest in ET brains that contain the most torpedoes.[72]

A number of other discrete structural changes have been observed in the cerebellar cortex in ET, and some of these changes are likely the reactive result of Purkinje cell loss in ET,[73] although this sequence of events remains to be definitively established. First, there is an increase in the number of heterotopic Purkinje cells in ET (i.e., Purkinje cells whose cell body is mislocalized in the molecular rather than Purkinje cell layer).[73] The mechanism underlying Purkinje cell heterotopia is not clear, but with the death of Purkinje cells, the immense Purkinje cell dendritic arbor disappears completely.[73] Such a situation could result in the remodeling of structures in the molecular layer, leading to defective Purkinje cell body localization (i.e., a dislocation of Purkinje cells).[82] The fact that the number of heterotopic Purkinje cells in ET correlates inversely with the number Purkinje cells supports such a sequence of events.[73]

Another likely form of plasticity is seen in the basket cell response to Purkinje cell loss. Erickson-Davis et al.[74] recently observed an unusual dense and tangled (what was termed “hairy”) appearance of the basket cell axonal plexus surrounding Purkinje cell soma in Bielschowsky-stained preparations of cerebellar cortical sections in ET cases. The observed

hypertrophic changes were inversely correlated with the number of Purkinje cells (i.e., greater Purkinje cell loss was associated with more basket cell changes).[74] The mechanism by which the hypertrophy of the basket cell axonal plexus occurs is unknown. One possible explanation is that the increased profiles observed in ET represent an accumulation of converging basket cell processes recruited from neighboring Purkinje cells that have been damaged or died.[74] Thus, the hypertrophied basket cell processes observed in ET might be converging on and reorganizing around remaining Purkinje cells.[79]

The remodeling of Purkinje cell axons, discussed above, likely leads to an intra-cortical re-wiring.[79] On a physiological level, this indicates the likely formation of aberrant synapses, and the creation of new/abnormal cortical circuits in ET.[90] The increased number of recurrent collaterals and terminal sprouts, in particular, likely establish synaptic contacts and produce abnormal feedback loops.[90] Thus, abnormalities in local intra-cerebellar circuits are likely important features of the pathogenesis of ET.[82] Additional circuit changes in the Purkinje cell-connected populations (Basket cells, neurons in the deep cerebellar nuclei) are likely to be of mechanistic importance as well.

Implications of the Cerebellar Degenerative Model of ET

The cerebellar degenerative model of ET has a number of important implications. First, it posits the existence of an as-yet unidentified molecular event that sets the cascade of observed cellular changes in the Purkinje cell population in motion. Hence, it suggests that advancing our understanding of ET will involve the identification of that/those molecular event(s). It rejects the notion that the primary event in the pathogenesis of ET is the electrical coupling of neurons in the inferior olivary nucleus. Stated in another manner, there is a cellular and molecular pathophysiology of ET and the disease is not just the result of an electrical disarrangement.

The Cerebellar Degenerative Model of ET – Caveats

As noted above, ET is heterogeneous on many fronts. The presence of pathological heterogeneity has also been noted.[72] Indeed, aside from the changes noted above, in the form of ET that has been referred to as “cerebellar ET”, a number of other changes have been noted in different subgroups of ET brains. First, a small number of cases have ubiquitinated inclusions in the brain along with cerebellar degeneration.[99] Second, some brains also have brainstem Lewy bodies in a pattern that is not consistent with incidental Lewy body formation and not consistent with the Braak staging scheme of Parkinson’s disease. These Lewy bodies are most concentrated in the locus ceruleus, a structure that makes direct synaptic connections with the Purkinje cell population. The unifying feature of all of these forms of ET is that the cerebellum is involved directly or secondarily, and they are all degenerative. But they do suggest different pathways to degeneration in ET.

Challenges to the Cerebellar Degenerative Model of ET

Some specific details of the new model have not been sorted out. The extent of Purkinje cell loss is one of these. Conflicting data are emerging, with one group reporting no Purkinje cell loss, yet much of the discrepancy could be methodological.[100]

One would expect that the longer the duration of symptoms, the more pronounced the morphological changes in the brain. Although some of the postmortem morphological changes in the ET brain clearly correlate with disease duration,[93] others do not. While at first glance this observation is concerning, there are a number of plausible explanations. In general, cerebellar response to injury leads to changes that are likely to be partly regenerative/compensatory while others are regressive/degenerative.[25, 79, 92] Thus, as has been observed in Purkinje cells in various settings,[90] some axonal changes likely represent abortive regenerative attempts that are later followed by degeneration.[79] Therefore, at any one time, the observed morphological changes in a given brain region likely represent a complex mélange of regenerative, aborted regenerative, and degenerative events.[25, 79] This mixed array of ambi-directional events is likely to make simple linear models of morphological counts by disease duration unrevealing.[79]

Unanswered Questions and Future Directions

Our understanding of ET, and its biological underpinnings, is clearly still in its infancy. There are also many unanswered questions and gaps that need filling in. What is the primary event or events? What are the molecular changes that are unleashed and how do they result in the axonal and other changes that are being observed in the ET cerebellum? What is the correct order of cellular/reactive events? What is the extent of rewiring in the cerebellar cortex? With the new cerebellar degenerative model, circuitry is important, but likely not as hypothesized in the olivary model; rather, the local intra-cortical cerebellar circuitry is more the issue. Yet the details need to be fully elaborated, and the role of cerebral cortical loops in terms of modulating the abnormal disease-linked cerebellar outflow needs further exploration. Furthermore, given the notion that ET is heterogeneous, how many different pathways to cerebellar degeneration are there in ET, and how are these similar to/different from some of those seen in the various spinocerebellar ataxias? Regardless of the various knowns and unknowns, we have seen a renewed empirical science behind the biology of ET, and in this sense, there has been real “progress on the biological front”.

Conclusions

Recent mechanistic research in ET has focused more attention on the cerebellum and the role it seems to play in disease pathogenesis. The research is grounded in clinical as well as neuroimaging studies, which both consistently implicate the importance of this brain region in ET. A change in recent years has been a move towards controlled studies of human postmortem tissue. Of interest is that these studies similarly find that the structural changes in most ET cases seem to be linked to this brain region, and furthermore, that the changes are of a degenerative nature. This work has led to a new disease model, the cerebellar degenerative model, which places this disease, and our understanding of the disease, within the larger framework of such diseases. This progress on the biological front, it is hoped, will eventually translate into treatment changes, making this an exciting time.

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Table 1

Problems with the olivary model of essential tremor

1	The model is purely conjectural and there is no evidence that the hypothesized processes are occurring in the human disease ET.
2	Pacemakers exist in numerous locations in the central nervous system (locus ceruleus, dorsal raphe nucleus, thalamus, and the cerebellum). Thus, olivary pacemakers are not unique, and there has been no attempt to explain why these rather than the numerous other pacemakers are posited to be patho-mechanistically relevant in ET.
3	The harmaline model is an animal toxin model of tremor rather than a model of the human disease, ET, which occurs in nature. Action tremor is a non- specific neurological sign, and is not the equivalent of the human disease ET. Also, harmaline-exposed animals develop an acute tremor that resolves after a few hours - it is a model of acute action tremor rather than chronic action tremor.

Table 2

Morphologic Changes Currently Identified in the ET Cerebellum

CERBELLAR COMPARTMENT	CEREBELLAR MORPHOLOGICAL CHANGE	FINDING (i.e., ET CASE *VS.* CONTROL DIFFERENCE)
Purkinje cell dendrite	Purkinje cell dendritic swellings	7.3x – 30x increase[70]
Purkinje cell body	Reduction in Purkinje cell linear density	30 – 40% reduction[71, 72]
	Empty baskets	1.5x increase (unpublished)
	Purkinje cell heterotopias	3x increase[73]
Purkinje cell axon	Purkinje cell torpedoes	6 – 7x increase[72]
	Purkinje cell axonal recurrent collaterals	2.3x increase[93]
	Purkinje cell axonal branching	2.2x increase[93]
	Purkinje cell terminal axonal sprouting	2.5x increase[93]
	Purkinje cell arciform axons	2.0x increase[93]
	Purkinje cell thickened axonal profiles	17% increase[93]
	Increase in Purkinje cell infraganglionic plexus	40% increase[93]
Basket cell axonal processes	Hairy baskets	5.2x increase[74]
	Elongated LINGO1 pinceau processes	2.4x – 4.4x increase[75]