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Re-thinking the biology of essential tremor: From models to morphology

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SUMMARY

Remarkably little has been written on the biology of essential tremor (ET), despite its high prevalence. The traditional pathophysiological model for ET, the olivary model, states that ET is a primary electrical/ /electrophysiological entity, the result of pacemaking neurons in the inferior olivary nucleus that begin firing in a coupled and rhythmic manner, and thus, through an abnormal olivo-cerebellar output, produce tremor. Though this model is based on several sound neurophysiological observations, there are major problems as well. Despite its shortcomings, however, the model persists. With the traditional focus in ET on clinical neurophysiology, there has been little research on pathological anatomy, cell biology, and molecular mechanisms, and over the years, there have been few alternatives to the olivary model. However, rigorous tissue-based studies have recently identified a series of structural changes in the ET brain, most of which are centered on the Purkinje cell and connected neuronal populations, and which may involve a partial loss of Purkinje cells. An implication of these newer studies is that ET could be degenerative. This shift in paradigm opens the door for research that aims to identify the primary set of molecular triggers and the cascade of molecular/cellular events that accompany this disease.

1. Introduction

Despite the high prevalence of essential tremor (ET), its biology has not been studied extensively and is not well understood. A PubMed search conducted in June 2013, crossing the terms "essential tremor" and "biology", yielded only 17 entries, three of which dealt with other diseases rather than ET (e.g., migraine, multiple sclerosis) and none of which included the term "biology" in the article title. Along similar lines, until recently, most textbook chapters did not include a discussion of tissue-based studies of ET.

Until recently, discussion of disease mechanisms in ET has been almost exclusively in the domain of clinical neurophysiology, with a focus on possible aberrant physiological loops. There has been little accompanying discussion of molecular mechanisms, cell biology, or pathologic anatomy, and little research focused on these issues.

The traditional pathophysiological model for ET is the olivary model. Over the past decade, an alternative model has arisen, namely, the cerebellar degenerative model of ET. Discussions of the biology of ET have thus moved beyond those that are limited to neurophysiological models to those that attempt to incorporate data from tissue-based studies as well. The purpose here is to review evidence that supports each of the current models of ET, and to broaden the discussion of disease mechanisms and biology.

2. Methods

The author used PubMed (1966 to May 2013) to cross search the terms "essential tremor" with additional search terms that were included, one by one: "biology", "pathology", "pathophysiology", "physiology", "inferior olive", "thalamus", and "red nucleus". All English language papers were reviewed. The author supplemented this review with published peer-reviewed articles in his files.

3. Results

Two models, the physiological (olivary) model and the cerebellar degenerative model will be reviewed.

3.1. Physiological (olivary) model

The olivary model is based primarily on three observations/tenets. First, the β-carboline alkaloids, including harmaline, harmine, harmane, and others, are a class of highly neurotoxic chemicals, and it has been known for 100 years that their administration to a broad range of laboratory species, including mice, cats, and monkeys, produces severe action tremor that resembles ET (Figs. 1a,b) [1]. It is posited that these toxins, through an excessive climbing fiber-derived glutamate discharge, result in Purkinje cell destruction.

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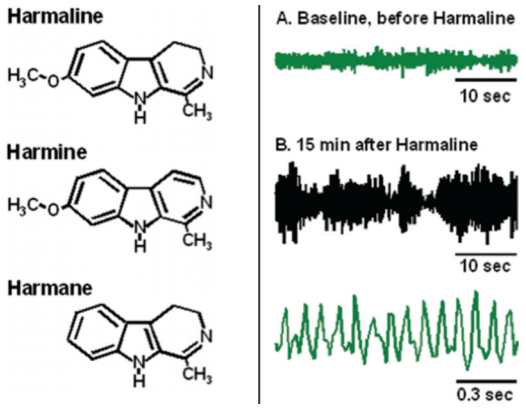

Fig. 1. Left panel: harmaline, harmine and harmane are β-carboline alkaloids that produce action tremor in laboratory animals. Right panel: Tremor induced by harmaline in a mouse model of tremor [2].

The second observation is that a variety of neurons in the central nervous system have pacemaking properties. That is, they can, under some circumstances, fire in a coordinated and rhythmical fashion. Among neurons with pacemaking properties are those in the inferior olivary nucleus (i.e., the climbing fibers). The third observation is that early studies on the pathology of ET concluded that there was no ET pathology. These studies were based on small numbers of cases, the complete absence of control brains for comparison, a cursory examination of the cerebellum, and no attempt to systematically assess or to quantify a broad range of microscopic findings in the cerebellum.

These three observations, when combined, provide the primary support for the olivary model, which states that ET is a primary electrical/electrophysiological entity. It is the result of pacemaking neurons in the inferior olivary nucleus that begin firing in a coupled and rhythmic manner, and thus, through an abnormal olivo-cerebellar output, produce tremor (Fig. 2).

The olivary model is both elegant and convenient, and it is based on sound neurophysiological observations. It also fits with the notion that the disease is one without strikingly obvious pathology. However, there are also major problems with the model. The first problem, and one that is not minor, is that there is no empirical evidence that this process is occurring in the human disease ET. In other words, the model is purely conjectural. As science is based on empirical evidence, this presents a sizable problem.

The second problem is that there are pacemakers in numerous and diverse locations in the central nervous system, including the locus ceruleus [3], dorsal raphe nucleus [4], thalamus [5], and cerebellum (Purkinje cells) [6]. Several of these areas also have connections with the cerebellum and/or are in the cerebellum. Hence, olivary pacemakers are not unique. There has been no attempt to justify why these rather than other pacemakers are held to be patho-mechanistically relevant in ET.

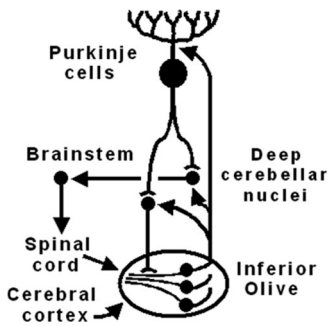

Fig. 2. The olivary model, which states that ET is the result of pacemaking neurons in the inferior olivary nucleus that begin firing in a coupled and rhythmic manner, and thus, through their olivo-cerebellar output, produce tremor [2].

A third problem with the olivary model is that its main empiric support comes from the harmaline model. The latter provides an example of abnormal olivary-cerebellar fiber output that is causing tremor. There are problems with the harmaline model and its application to ET. First, this is an animal toxin model of tremor **and not** a model of the human disease, ET, which occurs in nature. In the same way, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model is not the same as Parkinson's disease (PD), and experimental allergic encephalomyelitis (EAE) is not the equivalent of multiple sclerosis. Second, action tremor, which is the clinical product of harmaline administration, is a non-specific neurological sign, and is not the equivalent of the human disease ET. Thus, by analogy, just as *action tremor ≠ ET*, *weakness ≠ ALS*. Third, harmaline-exposed animals develop an acute, total body tremor of high frequency that resolves after a few hours. Hence, it is a model of **acute** tremor rather than chronic tremor.

A fourth problem with the harmaline model is that the massive, parasagittal destruction of Purkinje cells has not been observed as a postmortem feature of ET, indicating that the experimental results do not recapitulate the human disease. Furthermore, positron emission tomography studies, which began to emerge in the 1990s, did not demonstrate involvement of the inferior olivary nucleus in ET nor did later postmortem studies reveal structural changes in that nucleus [7], which further casts doubt on the putative role that this nucleus plays in the generation of ET.

Finally, there is the broad criticism of animal models that they do not take into account essential clinical characteristics of the disease such as the age of onset, the focal onset of clinical features, and the slow progression [8]. Moreover, animal models using toxins are invoking mechanisms that do not mimic pathologically relevant disease triggers in humans [8].

In summary, the olivary model of ET, though long-standing, and though having some attractive features, suffers from a number of critical problems. One must ask why this older model persists even in the face of little empiric proof. The only plausible explanation is that this seems to be an example of what scientific historians refer to as an established prejudice [9].

3.2. Cerebellar degenerative model

This model is based on the notion that ET is likely a neurodegenerative disease and that the focal point of that degeneration is the cerebellum itself. I will first review the clinical and epidemiological evidence that ET might be a degenerative type of disease and then will review the specific postmortem changes that have been observed in the ET cerebellum.

Critchley and Greenfield, as far back as 1948, wrote: "Although anatomical proof is as yet lacking, there are at least a number of clinical points to make [us] question whether "essential tremor" may not, at times any rate, represent an incomplete or a premature variant of one of the cerebellar atrophies" [10]. Thus, this idea that ET may be degenerative is not a new one, but it is one that has been given new life in recent years.

What is the clinical evidence that ET is neurodegenerative? First, like other neurodegenerative diseases (e.g., PD, Alzheimer's disease [AD]), ET has an insidious onset that is difficult to precisely pinpoint. For many years, the tremor may be dismissed by the patients themselves as just "nervousness". Second, like other neurodegenerative diseases, ET pursues a gradually progressive course that may continue for many years. Thus, as a rule, it is clinically progressive. Data from longitudinal studies indicate that the median rate of progression is on the order of 1.8–2.0% per year, and possibly higher [11]. Clinical experience suggests