Brief Reports

Harmaline-Induced Tremor in Mice: Videotape Documentation and Open Questions About the Model

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Abstract

Background: Harmaline-induced tremor in rodents has been extensively used as an animal model for essential tremor (ET). However, there is no visual documentation in the published literature.

Methods: We injected mice subcutaneously with either 20 mg/kg of harmaline hydrochloride or saline and then videotaped the responses.

Results: Action and postural tremor in the mouse began 5 minutes after subcutaneous harmaline injection and peaked at approximately 30 minutes. The tremor involved the head, trunk, tail, and four limbs and lasted for approximately 2 hours. The forelimb tremor was postural or action tremor, similar to that observed in ET.

Discussion: This video segment provides the first visual documentation of the phenomenology of harmaline-induced tremor in a mouse. We also raise several unanswered questions regarding the use of harmaline-induced tremor to model ET.

Keywords: Essential tremor, harmaline, mouse, cerebellum, inferior olive

Introduction

Essential tremor (ET) is the most common type of tremor, characterized by action and postural tremor in the upper extremities and/or neck and voice tremor.[1] The underlying mechanisms of ET have been extensively investigated. Genetic factors are important in ET, as it is common in kindreds.[2] However, the concordance in monozygotic twins is only about 60–63%,[3] indicating that environmental factors also play a role in ET.[4]

β-carboline alkaloids (BCAs), including norharman, harmane, harmine, harmaline, and ibogaine, are well known to induce action and postural tremor in mice, rats, rabbits, cats, and monkeys.[5–9] Exposure to exogenous BCAs seems to be associated with ET, as ET patients have higher levels of harmane in the blood and brain as compared to healthy controls.[10–15] Harmaline can induce tremor by the mechanism of synchronized firing in the inferior olivary nucleus (IO), leading to rhythmic activity within the olivocerebellar system, which has been hypothesized by some to be the anatomical substrate of ET.[16] Harmaline-induced tremor in animals is predominantly postural and action at the frequency of 8–14 Hz, similar to tremor in ET patients.[17,18] Furthermore, treatments for ET, such as β-blockers and primidone, can dampen harmaline-induced tremor.[18] These findings suggest that harmaline-induced rodent tremor models might be useful to investigate the mechanisms of ET.

Despite extensive research on harmaline-induced tremor in rodents, visual documentation of this tremor in published literature is lacking. The goal of the current study was to 1) provide video of harmaline-induced tremor in a mouse, 2) describe in detail the phenomenology of harmaline-induced tremor, 3) raise several unanswered questions regarding the use of harmaline-induced tremor to model ET.

Methods

We subcutaneously injected C57/BL6 mice with either harmaline 20 mg/kg or saline and observed tremor at rest, posture, and action.

Video 1. Harmaline-induced Tremor. Subcutaneous administration of 20 mg/kg harmaline induced whole-body tremor in a mouse, whereas the saline-injected control mouse had no tremor. The harmaline-treated mouse exhibited action tremor in the body and tail during locomotion, as well as forelimb postural and action tremor. The harmaline-treated mouse also had intermittent rest tremor. The control mouse did not have any action tremor or forelimb tremors.

Results

Five minutes after subcutaneous harmaline administration, we observed tremors at approximately 10–16 Hz, involving the head, trunk, and tail (Video). The tremor became more apparent during locomotion and occurred only intermittently at rest. The tremor lasted for approximately 2 hours. A head tremor was noted on elevating the head and was mainly seen as a vertical motion. The tail tremor was also mostly vertical. The forelimb tremor was seen when the animal reared and raised its forepaw. The hindlimbs also had tremor during locomotion. Control mice did not have any apparent tremors (Video). In addition, harmaline also caused slow locomotion, but these symptoms disappeared when the tremor resolved.

Discussion

We present the first visual documentation of harmaline-induced tremor in mice. We observed postural and action tremors, as previously reported.[8,17] In addition, we observed prominent forelimb postural tremors in harmaline-treated mice, which have not been described in detail.

Acute harmaline-induced tremors in rodents are a very useful animal model for ET research as they recapitulate disease phenotypes, and this report further supports this notion. Acute harmaline or ibogaine exposure in rats can also induce cerebellar Purkinje cell (PC) loss,[8,20] which is a major pathological feature of ET pathology.[21,22]

Harmaline and other BCAs can cause synchronization of rhythms in the IO and climbing fibers, which subsequently leads to PC dysfunction. ET, along with action tremors due to other causes, such as post-traumatic tremor, tremor of hyperthyroidism, and valproate-induced tremor, may share common anatomical tremor circuits with harmaline-induced tremor, and thus have similar pharmacological responses to treatment.[19] We observed mild unsteadiness in a harmaline-treated mouse during the period of tremor. However, whether harmaline can cause ataxic gait in mice requires further investigation. In addition, harmaline-treated mice also exhibited slow movements and locomotion, but these resolved with the resolution of tremor and were likely a secondary response to the tremor rather than bradykinesia per se. Thus, it is more likely that slowness is an aversive response to action and postural tremor[17] rather than a direct effect of harmaline on the basal ganglia.

There are several unanswered questions with regard to the use of harmaline-induced tremor to model ET. First, several postmortem studies found structural changes in the cerebellum, such as PC axonal torpedoes[22] and other associated axonal pathology,[23] basket cell axonal process changes,[24,25] and heterotopic PCs.[26] Acute effects of harmaline are unlikely to recapitulate these chronic pathological features of ET, although this remains to be determined. Second, the chronic effects of harmaline in terms of tremor characteristics and duration are poorly understood. Chronic administration of harmaline or other BCAs might be more useful in studying ET, especially for screening treatments that could prevent or reverse the pathological features of ET. The chronic effects of harmaline in mice have not been extensively investigated, and establishing a chronic harmaline tremor mouse model might be an important future research direction.

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