Pharmacological Characterization of Harmaline-Induced Tremors in Mice

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Introduction

Essential Tremor (ET) is one of the most common movement disorders which is thought to be twice as common as Parkinson’s disease. In general, ET is prevalent in the elderly and does not lead to serious complications. However, it has been shown that ET can be debilitating in a small percentage of patients.

Although the causes of ET are not known, genetics are thought to play a role in about 30-50% of ET cases. These genetic factors (ETM2) on 16q12.2, (ETM3) on 2q34, and (ETM4) on 4p22.1 have been identified as the familial form of ET. In addition, a function variant in the dopamine D3 receptor gene on 15q13 is thought to be a risk factor. (Dean et al., 2007; Higgins et al., 1994)

The neural circuitry underlying ET are not well understood either but positive emotion topography in breeds of ET patients revealed increased activity in the inferior olivary nucleus. Therefore, the localization of a circuit that may be responsible in ET pathology may be found by investigating gene loci for ET. These gene loci are thought to be involved in the regulation of serotoninergic and GABAergic receptors.

Animal models for ET are scarce. Two rodent models that are used to study ET are the hamster animal model and the GABA receptor alpha subunit knockout mice (Jankovic and Nothacker, 2003; Kristsch et al., 2005; Mala H 2007; Lorenzo and Deuschl 2007).

Harmaline is a -ketolcohol derivative that causes generalized tremor in mice with a frequency of 11 – 14Hz (Miller et al., 1995). Harmaline acts on the neurons of the inferior olivary nucleus (ION) to modulate their rhythm-generating ionic currents and thereby induce tremors. This effect can be attenuated by a variety of mechanisms including an indirect inhibition of the ION neurons. These mechanisms include the use of dopamine uptake blockers, GABA receptor antagonists, and GHB receptor agonists.

Hypothesis

GABAergic, glutamatergic and dopaminergic systems underlie some of the mechanisms of harmaline-induced tremors in mice.

Methods

Animals

Male ICR mice from Taconic Laboratories (Germantown, NY) were used in this study. Upon receipt, mice were assigned unique identification numbers (tail marked) and were group housed in CPTI mouse ventilation cages. All animals remained housed in groups of four during the remainder of the study. Mice were maintained on a 12 h light/dark cycle with food and water provided ad libitum for the duration of the study. Prior to testing, all mice were examined on a regular basis. Health and behavior were noted and mice were randomly assigned across treatment groups. Animals were not disturbed between tests.

Harmaline-induced tremors

Group housed mice were brought to the experimental room for at least one hour to acclimate prior to testing. Following a 20 min habituation period, mice were injected with water, propranolol or gabapentin (i.p) 20 min prior to harmaline injection. Data represent mean ± SEM. Using these parameters, tremor events are tabulated as short, long, total events and total time.

Statistical analysis

Data were analyzed using analysis of variance (ANOVA) followed by Fisher’s LSD post hoc test when appropriate. An effect was considered significant if p ≤ 0.05.

Results

The dopamine uptake blocker GBR12909 decreases harmaline-induced tremors in mice only at 2 mg/kg. The anticonvulsant agents gabapentin and valproate showed a dose-dependent attenuation of harmaline-induced tremors.

Discussion

These data support the findings of Kristsch et al. (2005), showing that harmaline-induced tremors is not mediated by the dopaminergic system.

Summary

In ICR mice, injection of harmaline produces tremors that are usually quantitated and induced by harmaline. These data support the findings of Kristsch et al. (2005) showing that tremors induced by harmaline are not mediated by the dopaminergic system.

These data suggest the involvement of multiple neurotransmitter systems in harmaline-induced tremors in mice. Further validation is needed to support a dopaminergic role in this test.

Nonetheless, harmaline-induced tremors in mice provide could be used as a model for screening novel therapeutic compounds for ET.

References