Published in final edited form as:

Mov Disord. 2008 January 30; 23(2): 259–264. doi:10.1002/mds.21829.

Paroxysmal Dyskinesias in Mice

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Abstract

Animal models of human disease are important tools for revealing the underlying mechanisms of pathophysiology and developing therapeutic strategies. Several unique mouse calcium channel mutants have been identified with nonepileptic, episodic dyskinetic movements that are phenotypically similar to human paroxysmal dyskinesias. In this report, video demonstrations of these motor attacks are provided for two previously described mouse mutants, tottering and lethargic, as well as a new one, rocker. Semiquantitative comparisons using two different rating scales reveal differences in attack morphology, severity, and duration among the strains. These mice provide three independent models of paroxysmal dyskinesia and support for prior proposals that channelopathies may underlie the human disorders.

Keywords

tottering; lethargic; rocker; paroxysmal dyskinesia; dystonia; channelopathy

The paroxysmal dyskinesias are a group of rare disorders characterized by intermittent attacks of involuntary abnormal movements.^{1–3} These movements are often dystonic or choreiform, but may include a variety of other abnormalities. Unlike epilepsy, they are not associated with abnormal activity on electroencephalograms (EEGs).

The paroxysmal dyskinesias are divided currently into three groups, which are based on the triggers of attacks, average attack duration, predominant morphology, and other features.^{1–3} Paroxysmal nonkinesigenic dyskinesia is precipitated by stress, caffeine, or alcohol. The frequency of attacks ranges from a few per day to a few per year, with a duration of a few hours to several days. In contrast, attacks of paroxysmal kinesigenic dyskinesia are brought on by sudden movement, startle, and even passive manipulation of muscles. They are more frequent but shorter, occur many times per day, and last less than a few minutes each. In paroxysmal exertional dyskinesia, attacks are caused by prolonged exercise. Attacks are of intermediate duration with a frequency tied to the level of physical exertion.

Recent studies also have revealed paroxysmal dyskinesias in certain strains of mice. The tottering mouse carries a mutation in the *Cacna1a* gene, which encodes a calcium channel subunit.^{4,5} These mutants exhibit mild ataxia at baseline with intermittent attacks of severely disabling dyskinetic movements.^{6,7} The lethargic mouse carries a mutation in the *Cacnb4* gene, which encodes a different calcium channel subunit.⁸ These mutants exhibit mild ataxia and a hypokinetic syndrome at baseline with intermittent attacks of dyskinetic movements.⁹ The purpose of this report is to provide a video demonstration of the motor phenotypes of tottering and lethargic mice. In addition, we describe paroxysmal dyskinesia in a third mutant mouse, rocker, which also carries a mutation in the *Cacna1a* gene, but different from that in tottering

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This article includes supplementary video clips, available online at <http://www.interscience.wiley.com/jpages/0885-3185/suppmat>.

mice.¹⁰ These mutant mice provide support for prior proposals that some forms of human paroxysmal dyskinesias may reflect a channelopathy.¹¹

MATERIALS AND METHODS

Animals

The tottering and lethargic mice used in these studies were obtained from the Jackson Laboratories (Bar Harbor, ME) while the rocker mice were obtained from Theresa Zwingman at Case Western Reserve University, Cleveland, OH. The tottering and rocker mutants were maintained on a C57BL/6J background, while the lethargic mutants were maintained on a C3H × C57BL/6J hybrid background. Mice were housed in groups of 2 to 12, and maintained on a 12-hour light–dark cycle with free access to food and water. Both male and female mice were evaluated as adults between 2 and 6 months of age. All animal procedures were conducted in accordance with institutional and National Institutes of Health guidelines for the treatment of experimental animals.

Motor Evaluation

Although there are many standardized tests of motor function for mice, none is well-suited for paroxysmal dyskinesias.¹² As a result, we adapted two parallel methods previously used for quantifying movement disorders in rodents. These methods are analogous to clinical rating scales developed for semiquantitative measures of abnormal movements and disability in human movement disorders.^{13,14}

In brief, mice were transferred from their home cages to individual clear plastic cages. They were observed directly for 60 seconds at 10-minute intervals for 2 hours, beginning 10 minutes after placement in the new cage. Two different rating scales were applied at each interval. A dyskinesia rating scale^{9,15,16} was used to describe the occurrence of different abnormal movements, and a disability scale¹⁷ was used to determine the overall functional impact of the abnormal movements.

For the dyskinesia scale, abnormal movements were recorded according to affected body part and included tremor (trunk, limbs, neck, and face), tonic flexion or extension (trunk, limbs, neck, and face), twisting (trunk and neck), clonus (limbs and face), head bobbing (vertical displacement), and head wagging (horizontal displacement). Several other motor problems not readily ascribed to an isolated body part were also recorded. These included falling (with all four limbs off the ground), listing (tilting to one side with two limbs off the ground), stumbling, widened stance, circling (360 ° turn with forward ambulation), spinning (360 ° turn without forward ambulation), and reverse locomotion. All abnormal behaviors were summed for each time point to generate a dyskinesia score that ranged from 0 to 30.

Motor disability was rated as follows: 0, normal motor behavior; 1, slightly slowed or abnormal behavior; 2, mild functional disability with transient abnormal postures and/or infrequent falls; 3, moderate functional disability frequent abnormal postures and/or frequent falls, but upright posture; and 4, severe functional disability with almost no ambulation, sustained abnormal postures and an inability to maintain an upright posture.

The dyskinesia and disability scores from separate attacks in each mutant strain (7 tottering, 7 lethargic, and 6 rocker animals) were used to compare several aspects of attack morphology between mutant strains. Attack severity was assessed by comparing maximum disability scores during the 2-hour observation period (peak severity), the sum of dyskinesia scores across all time bins (total dyskinesia score), and the time between departure from and return to baseline scores (duration). The contribution of movement types to the attack profile was determined by dyskinesia scores for specific types of abnormal movements as a percentage of the total

dyskinesia score for all abnormal movements. Body part involvement was similarly assessed. The frequency of spontaneous attacks was based on subjective estimates of the personnel caring for them. All statistical differences were determined by Mann–Whitney *U* tests.

Disability and dyskinesia scores were correlated well in all three strains with an r^2 of 0.82 for tottering, 0.72 for rocker, and 0.66 for lethargic. In addition, both scoring modalities demonstrated moderate agreement between two independent scorers with a linear weighted kappa of 0.63 for disability scores and 0.51 for dyskinesia scores.

RESULTS

Description of the Motor Disorder

Tottering (video 1)—Baseline motor function in tottering mice was nearly normal except for a slightly wide-based stance, clumsy limb placement, and a tremulous, unsteady gait. Attacks occurred in all mutant animals of both sexes and followed a characteristic pattern in the vast majority (~90%). Initially, animals exhibited jerky limb movements and increased ambulation and rearing. Next, the proximal hind limbs were retracted close to the body, the trunk assumed a dystonic, scalloped posture, and the pelvis approximated the cage floor. Distal hind limbs made clonic, paddling-like movements while head, neck, and forelimbs were relatively spared. Abnormal movements spread rostrally over 10 to 20 min, with writhing movements of the trunk followed by exaggerated, dystonic flexion of the head, neck, and jaw, as well as clonic pushing and twisting motions of the forelimbs. At peak severity, ambulation was impossible as the animal lay on its abdomen with periodic writhing of the whole trunk and repetitive but asynchronous limb activity. Attack resolution began with recovery of the rear limbs followed by recovery of the forelimbs. Attacks typically occurred 2 to 3 times per day and lasted more than 45 minutes.

Rocker (video 2)—Baseline motor behavior in rocker mice was indistinguishable from that of tottering mice. Attacks in rocker mice were similar to those of tottering with several exceptions. First, rather than affecting all mice, attacks in rockers were observed almost exclusively in adult females. Second, overall attack frequency was reduced compared to tottering and varied between individual female rocker mice, with some mice having frequent attacks and others few or none. Third, attacks in rocker mice were shorter than those of tottering mice, often lasting less than 45 minutes. Fourth, rocker attacks appeared to be less severe than those of tottering mice. Attacks often began with dystonic flexion of one limb, and exhibited limited spread before termination. Focal involvement of one limb was not uncommon. Segmental patterns were also frequent such as involvement of both forelimbs, one forelimb and the neck, or one half of the body.

Lethargic (video 3)—At baseline, lethargic mice displayed a notable lack of spontaneous movement. When active, motor activity tended to be bradykinetic and ataxic, with a wide stance and imprecise limb placement. Transient episodes of dyskinesia occurred in all animals of both sexes, and were most prominent in young animals. Attacks consisted primarily of dystonic movements of the limbs that occasionally involved the trunk, neck, and face. Like rocker, attacks were often focal or segmental. Attacks were more frequent than those in either tottering or rocker mice and often recurrent. They were also much shorter, typically lasting less than 5 minutes.

Quantitation of the Motor Disorder

Two methods were used to document quantitative differences among attacks of the three mutant mouse lines. Baseline dyskinesia and disability were low in all the three mutants, reflecting minor motor abnormalities at baseline. The characteristic temporal profile of attacks for each

mutant was evident in both the dyskinesia and disability scales (see Fig. 1). The temporal profile of tottering attacks was characterized by a peak at 40 to 60 minutes with a return to baseline by 90 to 120 minutes. Rocker attacks were less severe with a lower peak disability score and total dyskinesia score. Attacks also appeared to be shorter, but fell short of statistical significance ($P = 0.053$). The temporal profile of lethargic attacks lacked a single, obvious peak and was also less severe. This reflects the short duration of attacks,⁹ and the tendency for multiple short recurrent attacks during the 2-hour observational period.

The movement composition of tottering and rocker attacks showed a similar predominance of dystonic movements with less tremor and fewer clonic movements (Fig. 2A). Decreased attack intensity as reflected in the total dyskinesia score, and reduced clonic movements distinguished rocker from tottering. Dystonic movements were also the major constituent of dyskinesia in lethargic mice, with a frequency of clonic movements similar to tottering, and a near absence of tremor. Not surprisingly, an examination of dyskinesia in normal mice revealed almost no abnormal movements.

A similar analysis of body part involvement revealed a striking similarity among tottering, rocker, and lethargic mice (Fig. 2B). Forelimbs and hind limbs were the most affected body parts, accounting for ~70% of total abnormal movements, with a decreasing contribution of trunk, neck, and face.

DISCUSSION

These studies demonstrate paroxysmal dyskinesias in tottering, rocker, and lethargic mice. Each of these mutants harbors a mutation affecting the function of brain calcium channels, yet paroxysmal dyskinesias differed in each. Quantitative assessments reveal differences in severity, duration, and morphology. Tottering mice have the most severe and prolonged attacks. They are characterized by a predominance of generalized dystonic movements, with less clonic movements and tremor. Attacks in rocker mice are similar but less severe, shorter, and often focal or segmental rather than generalized. Attacks in lethargic mice are very brief and less disabling.

In addition to differences in the manifestations of attacks, there are differences in the factors that trigger attacks. A methodical investigation of triggers was not the purpose of the current studies, but prior studies have shown that tottering attacks are triggered by caffeine, alcohol, and stress.⁷ They do not appear to be triggered by exercise or motor stimulants such as amphetamine.¹⁸ In comparison, lethargic attacks are triggered by exercise and motor stimulants, in addition to mild stress.⁹ Triggers for attacks in rocker mice have not yet been explored, but preliminary studies indicate they include some of the same influences as tottering mice (unpublished).

It is notable that different mutations affecting the same calcium channel exhibit such distinct motor phenotypes in mice. In addition to paroxysmal dyskinesias with mild ataxia in tottering and rocker mice, other loss of function mutations in the mouse *Cacna1a* gene cause severe ataxia or generalized dystonia.^{19,20} A rat model with a missense mutation in the same gene also exhibits ataxia with a paroxysmal movement disorder.²¹ Though most of the rodent mutants are recessively inherited, semidominant or dominant phenotypes also occur.^{22,23} Human mutations in *CACNA1A* share a similar diversity of phenotypic outcomes. Mutations in this one gene have been linked with episodic or chronic progressive ataxia,²⁴ migraine headaches with or without hemiplegia,²⁵ benign paroxysmal torticollis of infancy,²⁶ epilepsy,²⁷ and focal or segmental dystonia in adults.²⁸ How these pleiotropic effects of *CACNA1A* dysfunction are manifested remains unclear.²⁹ It is likely that the different mutations affect calcium channel function in different ways, such as by altering gating properties, the rate of

calcium influx during channel opening, inactivation kinetics, ion sensitivity, trafficking to active sites, or compensatory changes in other channels.

Calcium channel mutant mice have previously been studied as models for absence epilepsy because of the existence of polyspike discharges on EEG.³⁰ The transient motor attacks superimposed upon a relatively normal baseline raise the possibility that these motor attacks are a form of motor epilepsy rather than a paroxysmal dyskinesia. However, several lines of evidence suggest that the motor attacks are not epileptic, but an independent aspect of the phenotype of calcium channelopathies. First, motor attacks are not accompanied by EEG changes suggestive of epilepsy in tottering,³¹ lethargic,⁹ or rocker (unpublished) mice. Second, antiepileptics do not suppress the motor attacks in any of these strains.^{7,9} Third, the duration of attacks in each strain is substantially longer than a typical tonic or tonic-clonic seizure that usually lasts less than 60 seconds. Fourth, the predominantly dystonic movements in these attacks contrast with the typical tonic-clonic movements of motor epilepsy. Together, these observations provide strong evidence that the motor attacks do not represent epilepsy. However, the co-occurrence of absence epilepsy and paroxysmal dyskinesias is not unexpected, as they often co-occur in affected humans.^{32–36} The mechanism is likely to involve disruption of calcium signaling in different brain regions responsible for epilepsy and paroxysmal dyskinesias.

Though rodents with neurological disorders cannot be expected to precisely match diagnostic categories established for humans, there are similarities between affected humans and mice. In both species, the predominant abnormal movement is dystonic, but with a combination of other abnormal movements. The triggers and duration of attacks in tottering and rocker mice most closely resemble paroxysmal nonkinesigenic dyskinesia, while the attacks of lethargic mice are closer to those of paroxysmal kinesigenic dyskinesia or paroxysmal exertional dyskinesia. These mice support prior proposals that paroxysmal dyskinesias might result from dysfunction of ion channels.¹¹ They also provide tools for exploring the pathogenesis and treatment of similar disorders in humans.³⁷

LEGENDS TO THE VIDEO

Segment 1

The first segment of this clip shows a tottering mouse at baseline. It walks and rears with a slightly tremulous and unsteady gait. The second segment shows the early phase of an attack involving predominantly the hind limbs and caudal body. The second segment shows full body involvement at the peak of an attack. The third segment shows the late phase of an attack with predominant involvement of the forelimbs, head, neck, and jaw (Adapted from Hess and Jinnah³⁸).

Segment 2

The first segment of this clip shows a rocker mouse at baseline with a tremulous and unsteady gait. The second segment shows a typical focal attack involving the right forelimb only. The third segment shows a segmental pattern involving both forelimbs and the neck, without progression to involvement of other body regions as in tottering mice. The third segment shows a pattern suggestive of hemidystonia with involvement of both limbs on one side and truncal torsion.

Segment 3

The first segment of this clip shows a lethargic mouse at baseline. It is slow and ataxic, but lacks the tremulous gait of the other two mutants. In addition to mild stress, attacks in lethargic mice are reliably induced by exertion as demonstrated in the balance of this clip. This segment

shows the baseline gait of a lethargic mouse on a treadmill. It is ataxic but able to maintain speed. The third segment shows a severe attack involving multiple body parts. The treadmill had to be stopped because the animal could no longer maintain a gait (Adapted from Devanagondi et al.16).

Acknowledgments

We thank Theresa Zwingman for the rocker mice. This work was supported by grants from the NIH (F32 NS52040, R01 NS40470, and R01 NS33592) and the Bachmann-Strauss Dystonia & Parkinson Foundation.

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FIG. 1.

Temporal profile of dyskinesias. Results show mean dyskinesia (A) and disability (B) scores $\pm$ SEM for 7 observed attacks in each strain. When compared to tottering by Mann-Whitney U test, peak severity scores were reduced in rocker ($P = 0.026$) and lethargic ($P = 0.001$) mice, while total dyskinesia scores were reduced only in rocker ($P = 0.017$). Attack duration in lethargic mice was shorter than in both tottering ($P < 0.001$) and rocker mice ($P < 0.001$).

FIG. 2. Contribution of abnormal movement type (**A**) and body part (**B**) to the total dyskinesia score. The contribution of clonic movements was reduced in rocker mice when compared to both tottering ($P < 0.001$) and lethargic ($P < 0.001$). Error bars are not shown in these stacked bar plots. The few abnormal movements observed in normal mice precluded their meaningful inclusion in (B).