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Pharmacology, Biochemistry and Behavior 73 (2002) 631–637

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Triggers of paroxysmal dyskinesia in the calcium channel mouse mutant tottering

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Received 18 January 2002; received in revised form 13 April 2002; accepted 26 April 2002

Abstract

Mutations in ion channels, or channelopathies, often lead to neurological disorders in which normal behavior is interrupted by attacks of debilitating symptoms such as pain, weakness or abnormal motor control. Attacks are often precipitated by similar stimuli, including stress, caffeine, ethanol, exercise or fatigue. The tottering mouse inherits a mutation in P/Q-type calcium channels and reliably exhibits attacks of abnormal movements, or dyskinesia. To determine if this mouse mutant is an appropriate model to study episodic neurological disorders, tottering mice were exposed to different environmental conditions or drugs known to precipitate attacks in humans. Stress, caffeine and ethanol all reliably induced attacks in tottering mice. Since calcium influx has previously been implicated in stress-induced tottering mouse attacks, the L-type calcium channel antagonist, nimodipine, and the NMDA receptor antagonist, MK 801, were tested for their ability to prevent attacks caused by caffeine or ethanol administration. Nimodipine blocked both caffeine- and ethanol-induced attacks, while MK 801 was effective against stress- and caffeine-induced attacks. These results support a common role for excess neuronal excitability and increased calcium influx in attacks triggered by diverse agents. Together, these results suggest that the tottering mouse is a novel model to investigate triggers of episodic neurological disorders.

Keywords: Channelopathy; Familial hemiplegic migraine; Episodic ataxia Type 2; Paroxysmal dyskinesia; Animal model; Stress; Tottering mice; Caffeine; Ethanol; Calcium channel

1. Introduction

Several neurological conditions share the unique feature of episodic expression of neuronal dysfunction superimposed on a normal baseline. These disorders include paroxysmal dyskinesia, periodic paralysis, episodic ataxia, hemiplegic migraine and common migraine, among others (Bhatia, 1999; Cooper and Jan, 1999; Demirkiran and Jankovic, 1995; Gardner and Hoffman, 1998; Jen, 1999; Ptacek, 1997, 1998, 1999). There is a growing consensus that the episodic nature of impairment in such disorders is related to transient dysfunction of ion channels, as many of these disorders are linked to mutations in genes encoding ion channels. Shared genetic etiology and transient attacks in these disorders classify them together as "channelopathies." Further, it was realized that co-occurrence of various features, such as migraine, epilepsy and movement disorders, can exist in subsets of patients with different channelopathies (Neville et al., 1998; Singh et al., 1999). While these disorders are rare, the pathogenesis of attacks in genetically 'simple' channelopathies may provide the basis for unraveling genetically complex episodic disorders such as migraine headache (Ptacek, 1998).

Though the symptoms of different channelopathies are quite diverse, many share common triggers such as psychological or emotional stress, fatigue, exercise, caffeine, alcohol, or hormonal fluctuations (Battistini et al., 1999; Boel and Casaer, 1988; Bressman et al., 1988; Cooper and Jan, 1999; Jarman et al., 2000; Jen, 1999; Lance, 1977; Mount and Reback, 1940; Pittock et al., 2000; Ptacek, 1998, 1999; Richards and Barnett, 1968). The existence of shared triggers suggests that they activate a common pathway that ultimately leads to expression of abnormal features. However, there is little understanding of the mechanisms by which these triggers precipitate neural dysfunction in an individual who is otherwise normal between attacks.

The transient nature of the neuronal dysfunction is a unique biological phenomenon that can only be addressed

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PII: S0091-3057(02)00854-7

in the awake, behaving animal. Mechanisms of attack induction in episodic disorders are difficult to investigate, largely because of the difficulty in experimentally producing similar features in animals. An animal model of episodic neuronal dysfunction could provide a powerful tool to examine the neurobiological basis of episodic neurological disorders, and may prove helpful in testing candidate drug therapies. The tottering mutant mouse displays an episodic movement disorder similar to paroxysmal dyskinesia (Campbell and Hess, 1999; Campbell et al., 1999; Green and Sidman, 1962), in addition to absence epilepsy (Kaplan et al., 1979; Noebels and Sidman, 1979). Like many human episodic disorders, the tottering syndrome is a channelopathy, resulting from a mutation within the gene encoding the α_1 subunit of P/Q-type calcium channels (Fletcher et al., 1996). Attacks of dyskinesia impair motor function in tottering mice approximately once or twice per day; between attacks, the mice are mildly ataxic but they otherwise exhibit normal motor behaviors. An attack in an adult tottering mouse lasts from 20 to 40 min and repeated attacks can occur with little to no refractory period. The mice do not lose consciousness, and the EEG appears normal during an attack (Kaplan et al., 1979; Noebels, 1984). Long regarded as spontaneous events, few reports have described stimuli that might trigger attacks in tottering mice.

Because the tottering mouse may be an important model for understanding episodic disorders, the behavioral profile of episodic dyskinesia in response to various stimuli reported to induce attacks in human channelopathy patients was studied. These stimuli included stress, exercise, caffeine and ethanol exposure. In addition, the role of calcium influx in the initiation of tottering mouse attacks was investigated using antagonists of L-type calcium channels and the NMDA receptor, a voltage- and ligand-gated calcium channel.

2. Materials and methods

2.1. Mouse mutants

Tottering mice were obtained from Jackson Laboratory (Bar Harbor, ME) and subsequently bred at the Johns Hopkins University School of Medicine. Tottering mice were identified by a slightly ataxic gait and attacks of dyskinesia. All tottering animals used in these experiments were between the ages of 2 and 6 months, and were group-housed based on age and sex. All experiments were performed during the light phase of the light/dark cycle. Animal procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Drug administration

Drugs were obtained from Sigma RBI (Natick, MA). Most drugs were dissolved in 0.9% saline. Phenytoin and carbamazepine were dissolved in dimethylsulfoxide, then diluted to 50% dimethylsulfoxide with 0.9% saline. Nimodipine was dissolved in a small volume of 100% ethanol and diluted with 5% ethanol, 2.5% Tween 80 and 0.9% saline. All injections were given subcutaneously in a volume of 10 ml/kg, except ethanol, which was delivered intraperitoneally.

2.3. Environmental triggers

Attack frequency and severity were recorded after subjecting tottering mice to various changes in their environment, in view of previous reports that anecdotally described increased attacks after environmental disturbance (Kaplan et al., 1979; Syapin, 1983). To determine a baseline attack frequency, tottering animals were observed in their home cages at 2 p.m. (7 h into the light cycle) under quiet conditions in the vivarium; mice were observed for 40 min and scored every 10 min for the presence or absence of attacks. Attacks induced by a change in the light cycle were recorded similarly from tottering mice observed in the vivarium in their home cages over 40 min immediately following the onset of the light cycle (7 a.m.). The effect of changing the home cage and transporting the animals to the laboratory was recorded during the 40 min immediately following transport. After a minimum of 2 h of acclimation, the mice were placed in novel cylindrical cages measuring approximately 4 in. in diameter and 5 in. in length, with wire mesh walls and wooden ends, for 10 min. The mice were scored for the presence of an attack in the novel cage and during the 40 min following release. After repeatedly exposing the mice to the cylindrical cages once per day for 4 days, the cages were set in motion at a speed of 2 rpm for 10 min to assess the effect of exercise on the frequency of attacks in tottering mice. To examine the effect of short-term restraint on tottering attacks, mice were placed in 60 cm^3 plastic syringes (modified for airflow) for 10 min, then observed for 40 min.

2.4. Drug triggers

For drug testing, mice were placed in clean cages, transported to the laboratory, weighed and then acclimated to the laboratory for a minimum of 2 h prior to the experiment. The mice were rated over 40 min for the presence of an attack following the injection of saline, caffeine or ethanol.

To determine if drugs effective against some human paroxysmal disorders and against tottering mouse absence seizures might be effective against the motor attacks, animals were pretreated with ethosuximide, phenytoin or carbamazepine and then exposed to a trigger. Mice were injected with the drug and observed for 30 min to allow time for the drug to reach the brain. However, if the drug itself was observed to cause attacks, the animals were not exposed to the trigger. Experiments using the calcium channel antagonists, nimodipine and MK 801, were performed in a similar manner.

2.5. Statistical analysis

Mice were scored once every 10 min for 40 min for the presence or absence of an attack following environmental disturbance or drug injection. Each mouse was assigned a total score, reflected by the number of times it received a positive score during the observation period (maximum score=4). These data were analyzed using the Mann–Whitney *U* test in the case of environmental disturbance, caffeine and ethanol administration, or with the Kruskal–Wallis nonparametric test for multiple independent groups when comparing total scores among several drug doses. Statistically significant differences (α=.05) among groups are noted in the figure legends. For ease of presentation, data are shown as total number and percent of tottering mice exhibiting an attack.

3. Results

3.1. Attacks

Attacks in tottering mice were often preceded by increased activity. The onset of an attack was signaled by contraction of the hindlimbs, causing a waddling gait but little change in mobility. As the attack progressed, the mouse lost mobility and began to slowly extend and contract the hindlimbs. Gradually, the upper limbs, head and neck exhibited severe flexion in addition to paddling movements of both hindlimbs. As the lower body recovered, the mouse assumed a tripod position on the hindlimbs and tail while the upper body was involved in extension/contraction movements, with frequent falls. These episodes continued over 20–40 min and were best characterized as paroxysmal dyskinesia.

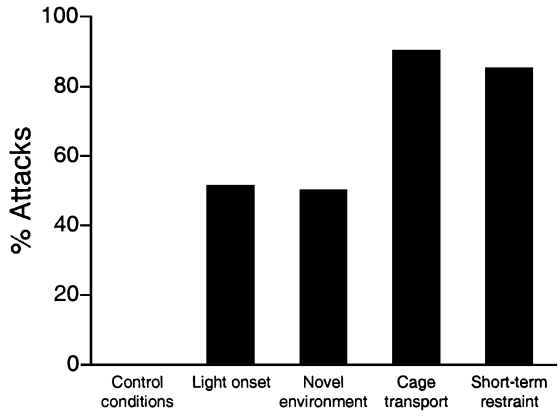

Fig. 1. Environmental disturbances trigger attacks in tottering mice. Baseline response was measured under control conditions (n=38) or after light cycle onset (n=37), cage transport (n=20), exposure to a novel environment (n=20) or short-term restraint (n=27). Data were analyzed using the Mann–Whitney nonparametric test and are shown as the percentage of mice exhibiting an attack. All environmental disturbances significantly promoted attacks (P<.0001) compared to control conditions.

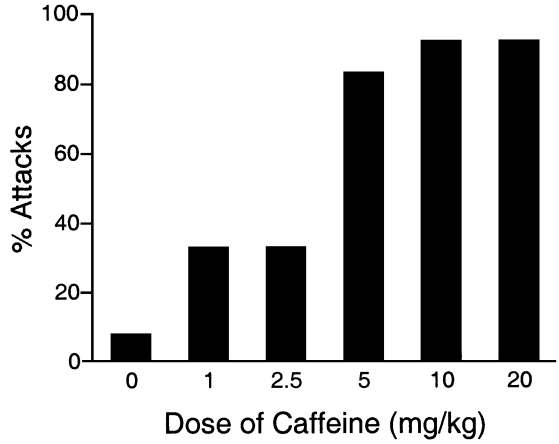

Fig. 2. Effect of caffeine administration on the frequency of tottering mouse attacks. Tottering mice (n=12/dose) were injected with caffeine (subcutaneously) or saline vehicle and observed for the onset of attacks. Data were analyzed using the Kruskal–Wallis nonparametric test and are shown as the percentage of mice exhibiting an attack. Caffeine significantly induced attacks in tottering mice (P<.0001).

None of the tottering animals had an attack during the undisturbed afternoon observation period (n=38), but 51.4% (19/37) of the tottering animals had an attack during the 40 min after the onset of the light cycle in the morning (Fig. 1). Following transport to the laboratory, 90% (18/20) of tottering animals had an attack. After acclimation to the laboratory, 50% (10 /20) tottering mice had an attack in response to exposure to the novel environment (cylindrical cages) for 10 min. Restraining tottering mice for 10 min precipitated attacks in 85% (23/27) of the mice, consistent with previous reports (Campbell and Hess, 1998, 1999; Campbell et al., 1999). All environmental disturbances significantly triggered attacks (P<.0001).

During 4 days of acclimation to the cylindrical cage, tottering mice exhibited attack frequencies ranging from 55% to 85%, suggesting that the mice did not habituate to the procedure during this time. On the fifth day, the same tottering mice were subjected to 10 min of exercise as the cylindrical cages were set in motion and the rotation of the cage forced the mice to maintain a slow but steady pace. Attacks were observed in 60% (12/20) of the mice following exercise, a frequency not significantly different from that observed when mice were simply exposed to the motionless cage for 10 min.

3.2. Drug triggers

Caffeine administration provoked attacks in tottering mice in a dose-dependent manner (Fig. 2; P<.0001). Ethanol also induced attacks; there appeared to be a threshold effect for ethanol whereby 0.2 and 0.5 g/kg did not induce attacks but all higher doses caused a significant increase in attacks

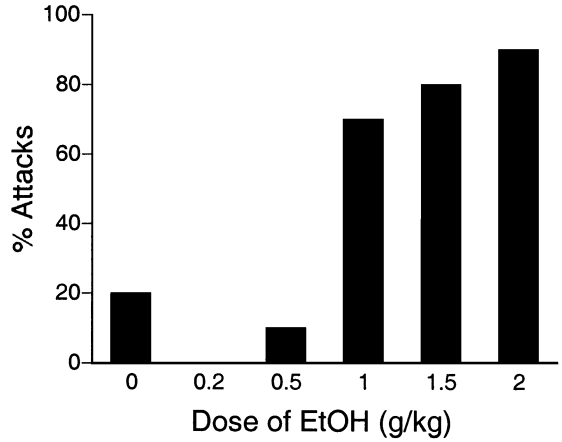

Fig. 3. Effect of ethanol administration on the frequency of tottering mouse attacks. Tottering mice (n=10/dose) were injected with ethanol (intraperitoneally) or saline vehicle and observed for the onset of attacks. Data were analyzed using the Kruskal–Wallis nonparametric test and are shown as the percentage of mice exhibiting an attack. Ethanol significantly induced attacks in tottering mice (P<.0001).

(Fig. 3; P<.0001). Latency to attack was comparable for caffeine and ethanol, suggesting that the effects of ethanol were direct and not due to a rebound after metabolism. The attacks induced by caffeine and ethanol were indistinguishable from those induced by other methods.

3.3. Potential therapeutics

Tottering mice were pretreated with drugs known to be effective against absence seizures (Heller et al., 1983) and/or certain episodic disorders (Demirkiran and Jankovic, 1995) to determine if they would prevent attacks. Ethosuximide and phenytoin tended to increase the frequency of attacks (Fig. 4), while attacks were significantly induced by carbamazepine (Fig. 4; P<.01). Therefore, mice were not exposed to a subsequent trigger.

3.4. Calcium-mediated effects

L-type calcium channel blockers, such as nimodipine, were previously shown to block tottering mouse attacks triggered by restraint (Campbell and Hess, 1999). Nimodipine also blocked attacks provoked by caffeine (P<.01) and ethanol (P<.001; Fig. 5).

The noncompetitive NMDA receptor antagonist, MK 801, which also blocks calcium entry into the cell, prevented stress-induced attacks in a dose-dependent manner (Fig. 6; P<.05). MK 801 pretreatment prevented caffeine-induced attacks (P<.01) but was ineffective against attacks triggered by ethanol (Fig. 7). Because the severity of ataxia in tottering mice appeared to increase at the highest dose of MK 801 used (0.2 mg/kg), consistent with previous reports in rats (Haggerty and Brown, 1996), tottering mice were pretreated with a lower dose of MK 801 (0.1 mg/kg) to avoid this side effect prior to caffeine or ethanol exposure. It is possible that higher doses of MK 801, which produce undesirable side effects, may block ethanol-triggered attacks.

4. Discussion

Many human disorders in which patients exhibit episodic attacks between periods of relatively normal behavior have

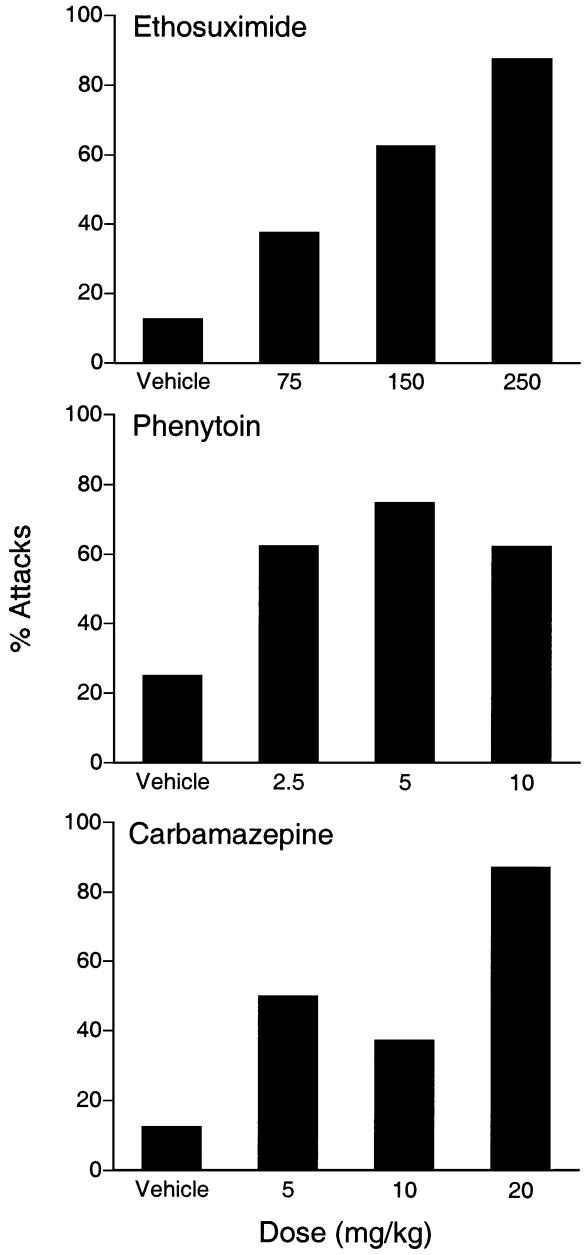

Fig. 4. Effect of anticonvulsant administration on the frequency of attacks. Tottering mice (n=8/dose) were injected (subcutaneously) with ethosuximide, phenytoin, carbamazepine or the appropriate vehicle and observed for the onset of attacks. Data were analyzed using the Kruskal–Wallis nonparametric test and are shown as the percentage of mice exhibiting an attack. Carbamazepine significantly induced attacks in tottering mice (P<.01), while ethosuximide and phenytoin exhibited similar trends.

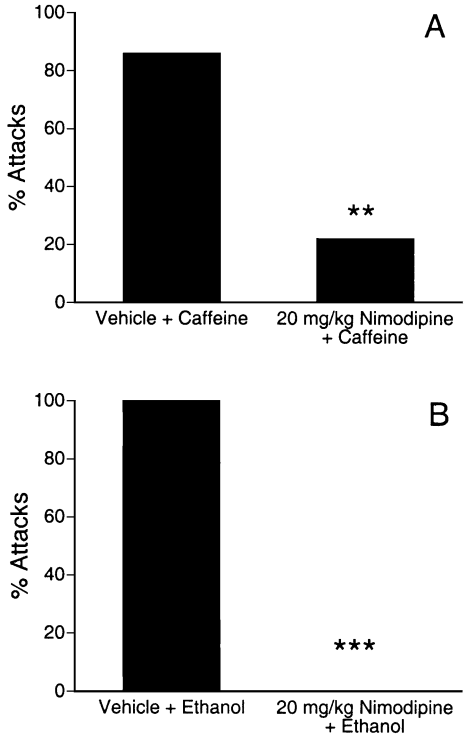

Fig. 5. Effect of nimodipine pretreatment on caffeine–ethanol-induced tottering attacks. (A) Tottering mice were pretreated with nimodipine (20 mg/kg) or vehicle 30 min prior to caffeine injection (15 mg/kg). Nimodipine pretreatment significantly prevented attacks triggered by caffeine (**P<.01). (B) Tottering mice were pretreated with nimodipine (20 mg/kg) or saline 30 min prior to ethanol injection (1.5 g/kg). Nimodipine pretreatment significantly prevented attacks triggered by ethanol (***P<.001). Data are expressed as the total number and percentage of mice exhibiting an attack within 40 min of exposure to the trigger.

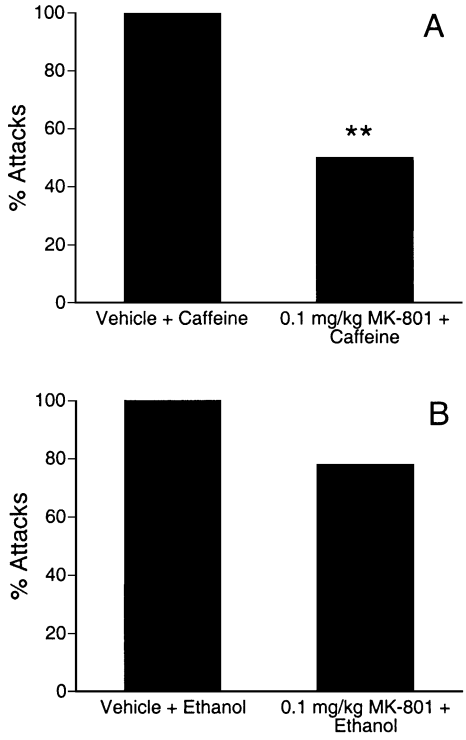

Fig. 7. Effect of MK 801 pretreatment on caffeine- and ethanol-induced tottering attacks. (A) Tottering mice were pretreated with MK 801 (0.1 mg/kg) or vehicle 30 min prior to caffeine injection (15 mg/kg). MK 801 pretreatment significantly prevented attacks triggered by caffeine (**P<.01). (B) Tottering mice were pretreated with MK 801 (0.1 mg/kg) or saline 30 min prior to ethanol injection (1.5 g/kg). MK 801 pretreatment did not significantly prevent attacks triggered by ethanol. Data are expressed as the total number and percentage of mice exhibiting an attack within 40 min of exposure to the trigger.

been linked to mutations in genes encoding ion channels (Ptacek, 1998). Interestingly, the features of these seemingly diverse disorders are often triggered by similar phenomena,

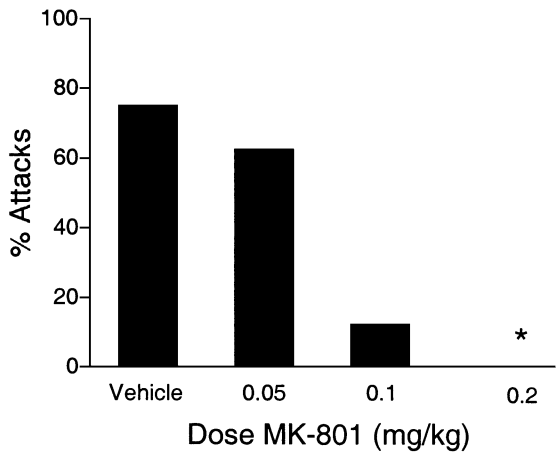

Fig. 6. Effect of MK 801 on restraint-induced tottering mouse attacks. Tottering mice (n=8–9/dose) were injected with MK 801 (subcutaneously) 30 min prior to restraint. Data were analyzed using the Kruskal–Wallis nonparametric test and are shown as the percentage of mice exhibiting an attack. MK 801 significantly prevented restraint-induced attacks (*P<.05).

such as psychological or emotional stress, exercise, fatigue, caffeine, alcohol and hormonal cycles in women. A newly emerging concept is that despite apparent differences in the overt manifestations of individual disorders, channelopathies as a group may share common underlying disease mechanisms, particularly with regard to precipitating factors. The present results show that the tottering mouse provides a unique model with which to study the action of various triggers on perturbed ion channel systems.

Similar to human episodic disorders, caffeine, ethanol and stress reliably induce attacks in tottering mice. The biological actions of the precipitants themselves are currently the only clues to the events underlying the onset of an attack. Caffeine, ethanol and stress exert a wide variety of effects on the central nervous system, ranging from behavioral deficits in fine motor control with acute ethanol ingestion to changes in gene expression mediated by stress hormones. Additionally, these triggers have direct effects on neuronal excitability, although not necessarily in the same direction, as caffeine is regarded as a central nervous system stimulant while ethanol is a depressant. At physiologic levels, caffeine exerts its stimulatory effects by acting as an antagonist at adenosine receptors to block the inhibitory

effects of adenosine (Fredholm et al., 1999). Other actions of caffeine, particularly the release of calcium from intracellular stores via ryanodine receptors, blockade of $GABA_A$ receptors and the inhibition of cyclic nucleotide phosphodiesterases are unlikely to occur at the doses attained during normal human consumption. In contrast, acute intoxicating levels of ethanol depress synaptic transmission, likely by reducing excitatory inputs and enhancing inhibitory inputs through effects on selected ion channel subtypes (Nestoros, 1980; Lovinger et al., 1990; Lewohl et al., 1999).

The disparity in the acute effects of physiological doses of caffeine and ethanol suggest that these substances should have opposite effects on the initiation of symptomatic attacks in channelopathy patients. One possible explanation is that the destabilizing influences of caffeine or ethanol on the neuronal membrane, regardless of the direction on excitability, are sufficient to trigger the network abnormalities that manifest as symptomatic attacks. However, an alternative explanation is that caffeine and ethanol share a common biological mechanism; administration of both generates a neuroendocrine response analogous to a stress-like activation of the hypothalamic–pituitary–adrenal axis (Ellis, 1966; Nicholson, 1989; Pollard, 1988; Rivier et al., 1984).

Calcium channels are likely to be a critical part of a common pathway. L-type voltage-dependent calcium channels were previously implicated in the pathophysiology of attacks in tottering mice, since administration of L-type calcium channel antagonists inhibits restraint-induced attacks whereas L-type calcium agonists induce attacks (Campbell and Hess, 1999). In the present study, the L-type calcium channel antagonist, nimodipine, was effective in preventing attacks precipitated by caffeine or ethanol administration. The noncompetitive NMDA receptor antagonist, MK 801, was also effective at preventing restraint- and caffeine-induced attacks. NMDA receptors are voltage- and ligand-gated calcium channels responsive to glutamate. The inhibition of attacks with MK 801 demonstrates that decreasing neuronal excitability and calcium influx through a second calcium channel type can also prevent attacks. Overall, these results suggest that stress, caffeine and ethanol initiate attacks via mechanisms dependent on altered neuronal excitability and increased calcium influx, further supporting the idea that a final common pathway exists between diverse triggers in this model of episodic neurological dysfunction.

The tottering mouse is also studied as a model of absence epilepsy, owing to periodic polyspike bursts in the EEG accompanied by behavioral arrest (Kaplan et al., 1979; Noebels and Sidman, 1979). Absence epilepsy and paroxysmal dyskinesia in tottering mice are likely independent phenotypes, a distinction supported by the results of the present study. The anticonvulsant, ethosuximide, which reduces calcium current through low voltage-activated calcium channels, prevents absence seizures in tottering mice (Heller et al., 1983) but offers no therapeutic value in preventing attacks of dyskinesia. Additionally, the antiepileptic drug, carbamazepine, which blocks sodium channels, actually promoted tottering mouse attacks at higher doses. Surprisingly, caffeine blocks absence seizures (Kostopoulos et al., 1987) but potently induces attacks of dyskinesia, possibly via antagonist actions at inhibitory adenosine receptors. It is not yet clear how these particular drugs influence excitability in membranes altered by the tottering mutation in P/Q-type calcium channels, but patients with similar movement disorders are also often unresponsive to typical anticonvulsant therapies (Demirkiran and Jankovic, 1995). The results suggest that attacks of dyskinesia in tottering mice are clearly pharmacologically and perhaps mechanistically dissociated from the polyspike discharges although the primary cause of both phenotypes is the P/Q-type calcium channel mutation. Differences in ion channel and receptor subtype distribution in the brain regions critical for the expression of attacks and absence seizures are likely to explain, at least in part, this phenotypic dissociation.

Although the clinical presentation has historically divided most channelopathies into movement disorders, migraine headache disorders or muscle disorders, more recently the clinical boundaries between different episodic disorders have become blurred. There is a growing awareness that co-occurrence rates of epilepsy, migraine, periodic paralyses and paroxysmal movement disorders are somewhat higher than might be expected due to chance (Demirkiran and Jankovic, 1995; Gardner and Hoffman, 1998; Hofele et al., 1997; Ptacek, 1998, 1999; Singh et al., 1999). The co-occurrence of epilepsy and a paroxysmal movement disorder in mice is remarkably consistent with recent reports of subsets of channelopathy patients exhibiting more than one type of episodic disorder (Demirkiran and Jankovic, 1995; Neville et al., 1998; Singh et al., 1999). Overall, the similarities in genetic etiology, precipitating factors and overlap in symptomology in both mouse and man suggest that ion channelopathies may present a heterogeneous group of disorders with common underlying triggering mechanisms. Tottering mice, arising from a mutation in a neuronal calcium channel, are one of few genetic animal models that recapitulate the transient nature of episodic disorders with symptoms triggered by stress, caffeine and ethanol. As such, tottering mice offer a new avenue of research into the link between ion channelopathies and triggers of episodic disorders.

Acknowledgments

We thank Roger S. Carroll for technical assistance. This work was supported by PHS NS33592, NS34845 and NS40470.

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