# A Consensus Definition of Cataplexy in Mouse Models of Narcolepsy

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People with narcolepsy often have episodes of cataplexy, brief periods of muscle weakness triggered by strong emotions. Many researchers are now studying mouse models of narcolepsy, but definitions of cataplexy-like behavior in mice differ across labs. To establish a common language, the International Working Group on Rodent Models of Narcolepsy reviewed the literature on cataplexy in people with narcolepsy and in dog and mouse models of narcolepsy and then developed a consensus definition of murine cataplexy. The group concluded that murine cataplexy is an abrupt episode of nuchal atonia lasting at least 10 seconds. In addition, theta activity dominates the EEG during the episode, and video recordings document immobility. To distinguish a cataplexy episode from REM sleep after a brief awakening, at least 40 seconds of wakefulness must precede the episode. Bouts of cataplexy fitting this definition are common in mice with disrupted orexin/hypocretin signaling, but these events almost never occur in wild type mice. It remains unclear whether murine cataplexy is triggered by strong emotions or whether mice remain conscious during the episodes as in people with narcolepsy. This working definition provides helpful insights into murine cataplexy and should allow objective and accurate comparisons of cataplexy in future studies using mouse models of narcolepsy.

**Keywords:** Orexin, hypocretin, atonia, REM sleep, paralysis, positive affect

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MANY RESEARCHERS ARE NOW STUDYING MOUSE MODELS OF NARCOLEPSY, BUT DEFINITIONS OF CATAPLEXY-LIKE BEHAVIOR IN THESE MICE DIFFER across labs. This commentary is the product of a workshop held in November 2007 by the International Working Group on Rodent Models of Narcolepsy. This meeting established a consensus working definition of murine cataplexy. We hope this common language will be useful for researchers working with mouse models of narcolepsy and for clinicians seeking a better understanding of cataplexy and of narcolepsy in general.

## CATAPLEXY IN HUMAN NARCOLEPSY

Cataplexy has long been recognized as the pathognomonic symptom of narcolepsy.[1] It usually begins a few months after the onset of narcolepsy and is sometimes the presenting symptom.[2] Cataplexy is a sudden loss of muscle tone triggered by strong emotions, especially laughter, joking, surprise, or elation, and more rarely, anger or grief.[3] The atonia may involve all skeletal muscles, but frequently, it is partial with transient face and neck weakness or slurred speech. At the onset, the lapses in tone can be intermittent like asterixis, resulting in jaw tremor or knee buckling. The eyes may be closed, but voluntary eye movements are preserved.[4]

The loss of tone usually lasts < 2 min and is accompanied by loss of deep tendon reflexes and the monosynaptic H-reflex.[5] Most often, patients with postural collapse avoid injury as the fall is slow and progressive. Cataplexy may be more severe in young children, and its frequency often decreases with age.[6,7] During cataplexy, people remain fully awake and conscious,[8] though some attacks can include hypnagogic hallucinations and with rare attacks of long duration, subjects may enter REM sleep.[9] Cataplexy can occur at any time of day.[10]

Over 90% of people with cataplexy have low or undetectable levels of the orexin/hypocretin neuropeptides in lumbar cerebrospinal fluid (CSF).[11] This finding is in concordance with neuropathologic studies showing a marked and selective loss of the orexin-producing neurons in the lateral hypothalamus.[12-14] In contrast, orexin-A (hypocretin-1) levels in CSF are usually normal in narcolepsy *without cataplexy* and in idiopathic hypersomnia, highlighting the strong connection between orexin deficiency and atonia.[11]

Cataplexy is strongly associated with specific HLA markers. Among patients with clear-cut cataplexy, 88 to 98% are DQB1*0602 positive across a variety of ethnic groups.[15] Clinically, cataplexy often improves substantially with medications that block norepinephrine reuptake.[16] Tricyclic antidepressants such as protriptyline and clomipramine were the traditional drugs for treating cataplexy, but their anticholinergic side effects have limited their use. The newer monoamine reuptake inhibitors such as fluoxetine and venlafaxine have become drugs of choice as they have fewer side effects. More recently, sodium oxybate (gamma-hydroxybutyrate) taken at bedtime and during the sleep period, has shown great efficacy on cataplexy,[17] though its mechanism of action remains unknown.

## CATAPLEXY IN NARCOLEPTIC DOGS

Cataplexy in dogs closely resembles human cataplexy in many ways.[16,18,19] Canine cataplexy is typically elicited by play

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with other dogs or with human caretakers; catching or retrieving objects, and tugging on towels or sticks are particularly effective triggers. Copulation will often elicit cataplexy in male narcoleptic dogs. Cataplexy can also be readily elicited by eating, particularly if the food is especially favored.[16,20] In fact, narcoleptic dogs usually have about 2 episodes of cataplexy/hour during the day, but during the Food Elicited Cataplexy Test, they can have 5 or more episodes in just 1 or 2 minutes.[21,22] In contrast, canine cataplexy is not triggered by startling loud noises, and it is suppressed by exposure to new individuals or an unfamiliar room.

Cataplexy in dogs typically exhibits a progression of muscle tone suppression, with the hindlimbs often affected first.[23] The hindlimb weakness often resolves in a few seconds during partial cataplexy, or it can spread to the forelimbs and axial muscles producing generalized weakness. Occasionally, the forelimbs and hindlimbs collapse simultaneously.[23] Even after the animal collapses to the ground, it may continue to eat, demonstrating preservation of tone in the cranial muscles, though in a full attack, even these muscles become atonic. Roughly 80% to 90% of the time, the eyes are open at the start of cataplectic attacks, and the eyes will track objects of interest,[24] suggesting that dogs, like humans, maintain consciousness during cataplexy. Attacks usually last for a few seconds, but can continue for several minutes.[21,22] Long attacks may progress into a state much like REM sleep with closure of the eyes, rapid eye movements, and distal muscle twitching.[19] In contrast to REM sleep, canine cataplexy can occur at any time of day.[21]

Studies of neuronal activity during cataplexy, REM sleep, and waking reveal underlying similarities and differences between these 3 states. Most neurons in the reticular formation of the pons and medulla, which likely employ amino acid neurotransmitters, show repetitive phasic activation during REM sleep but reduce their activity or are silent during cataplexy.[25] These cells may have a role in mediating the twitches that are seen in REM sleep,[26-28] but which are absent or minimal in cataplexy. On the other hand, a population of neurons in the medial medullary reticular formation that suppress muscle tone are tonically active during cataplexy at levels similar to those seen in REM sleep.[25] Noradrenergic neurons in the locus coeruleus can facilitate muscle tone during waking, but these cells fall silent during REM sleep and cataplexy.[29] In contrast, wake-promoting histaminergic neurons are inactive during REM sleep but are active during cataplexy.[30] Orexin neurons have direct projections to both histaminergic and noradrenergic neurons,[31] and loss of orexin signaling may cause cataplexy through a loss of coordination in these cell groups. Specifically, during cataplexy, inactivity of noradrenergic cells may disinhibit the medial medullary REM-on neurons that promote atonia, whereas consciousness may be preserved by persistent activity in histaminergic neurons.[32-34] The neural pathways that mediate the triggering of cataplexy are less clear, but neurons in the amygdala (basal magnocellular and central nuclei), a region strongly involved in the expression of emotions and projecting to brainstem regions, are activated during cataplexy.[35]

Pharmacologic observations fit well with these patterns of neuronal activity. Canine (and human) cataplexy is worsened by the noradrenergic alpha-1 antagonist prazosin and is improved by drugs that increase noradrenergic signaling.[16,36] Canine cataplexy can also be intensified by the cholinesterase inhibitor physostigmine, a compound that suppresses motor tone when microinjected into atonia-promoting brainstem regions.[24,37]

Other aspects of physiology have been studied in the narcoleptic dog. Hippocampal theta activity is high during cataplexy, just as seen during REM sleep and active waking.[30] Heart rate accelerates prior to spontaneous cataplexy attacks and decelerates at the beginning of cataplectic episodes.[18] Similar heart rate changes do not occur at REM sleep onset. Prolonged canine cataplexy also may be accompanied by apneas and erections.[38-41]

## CURRENT KNOWLEDGE OF MURINE CATAPLEXY

Well-characterized mouse models of narcolepsy with cataplexy have been produced with deletion of the *prepro-orexin* gene[42] and with transgenic expression of a toxic protein that selectively kills the orexin-producing neurons.[43] These mice have cataplexy-like behavioral arrests, poor maintenance of wakefulness, and fragmented sleep.[42-45]

Cataplexy in mice shares many similarities with human cataplexy (Table 1).[42-44,46] At the onset, the mouse abruptly ceases vigorous motor activity and often has a staggering gait probably caused by asterixis (brief lapses in muscle tone) (Supplemental video).[44] The mouse then collapses prone, sometimes falling to its side for 30 sec to 2 min, a duration remarkably similar to human and canine cataplexy.[42-45] Toward the end of an episode, mice sometimes have rhythmic hindlimb activity that rocks their bodies. At the end of an episode, the mouse rapidly recovers normal tone and often resumes vigorous activity.[47] These behavioral arrests almost always occur during active wake and are often preceded by running, climbing, grooming, exploring, or social interaction, suggesting they may be triggered by strong emotions. Narcoleptic pups may have more frequent behavioral arrests than adults (J. Willie, unpublished observations). Preliminary observations suggest that narcoleptic mice are awake during arrests, with open eyes and weak withdrawal from threatening visual stimuli.[44] In addition to these behavioral similarities with human cataplexy, behavioral arrests in mice are suppressed by the prototypical anti-cataplectic agent clomipramine.[44]

The appearance of cataplexy helps distinguish it from similar behaviors. During cataplexy, the mouse often collapses prone or on its side, whereas during normal sleep the mouse assumes a curled posture in its nest area. Cataplexy occurs abruptly during active wake, but rapid transitions into NREM sleep ("sleep attacks") have a more gradual onset during quiet wake.[42,44]

Additional observations suggest that emotions can trigger murine cataplexy. Cataplexy is more frequent with social interaction and environmental enrichment with novel toys, fresh bedding, running wheels, or an open field.[42,47,48] Mild fasting, restricted feeding schedules, and consumption of highly palatable food all increase rates of cataplexy,[44,49] but none of these techniques seem to provoke the instantaneous cataplexy observed in dogs during the food-elicited cataplexy test.[16,48] Also in contrast to dogs, preliminary observations suggest that cataplexy is uncommon in mice during sexual activity (J. Willie, E. Clark, unpublished observations). Most of these observations on triggers of murine cataplexy are preliminary, and more work

**Table 1**—Cataplexy Across Species

| | Human | Dog | Mouse |
|---|---|---|---|
| Behavioral features | Abrupt loss of postural muscle tone | Abrupt loss of postural muscle tone | Abrupt loss of postural muscle tone |
| Level of consciousness | Awake (memory of episodes intact) | Probably awake (visual tracking intact) | Uncertain, but possibly awake at onset (response to visual stimuli intact) |
| Triggers | Strong, generally positive emotions (e.g. laughter, joking, playing) immediately before cataplexy | Probably positive emotions (e.g. playing, eating palatable food) immediately before cataplexy | Active behaviors with likely emotional content (e.g. running, climbing, vigorous grooming, social interaction) |
| Duration | Brief (seconds to a few minutes) | Brief (seconds to a few minutes) | Brief (seconds to a few minutes) |
| EEG | Wake pattern and sometimes features of REM sleep | Wake pattern in cortex with theta activity in hippocampus | Theta activity similar to REM sleep |
| EMG | Atonia, sometimes with intermittent lapses in tone at onset | Atonia, sometimes with intermittent lapses in tone at onset | Atonia, sometimes with intermittent lapses in tone at onset |
| Response to therapy | Suppressed by monoamine reuptake blockers (e.g. antidepressants) and sodium oxybate | Suppressed by monoamine reuptake blockers | Suppressed by clomipramine |

Cataplexy has many similarities in people, dogs, and mice with narcolepsy including abrupt postural atonia and improvement with clomipramine. During cataplexy in people and dogs, some authors report an EEG pattern similar to wake while others describe characteristics of REM sleep, despite preservation of consciousness. See text for supporting references.

is needed to determine whether murine cataplexy is triggered by emotions.

Physiologically, murine cataplexy shares many features with REM sleep. As a mouse transitions from active wake into cataplexy, the EEG changes from a typical waking pattern to one indistinguishable from REM sleep or the pre-REM sleep spindling often seen in mice.[42-44] Once cataplexy is fully established, the EEG is dominated by high amplitude theta activity with an EEG power spectrum much like REM sleep.[44,45] Most likely, this theta activity during cataplexy is generated in the hippocampus, but this has not yet been confirmed with depth electrode recordings. It is unclear whether sustained murine cataplexy evolves into REM sleep as has been reported for some episodes of human cataplexy.[9,49]

Genetic factors and recording conditions may alter the frequency of cataplexy. Cataplexy occurs about four times more often in narcoleptic mice on a DBA/2 background compared to those on a C57BL/6 background.[50] (and T. Sakurai and J. Willie, unpublished observations) In addition, murine cataplexy may be suppressed by handling or other stressors (J. Willie, unpublished observations). Uninstrumented orexin knockout mice in open fields can have about 15-20 behavioral arrests in the first 4 hours of the dark period,[42,44] whereas instrumented mice tethered with lightweight recording cables and low torque commutators in their home cage have about 20 episodes over the 12-h dark period.[45,47] Whether this difference in event frequency is due to tethering, differences in genetic background, or recording environments remains unclear. Still, even in humans, cataplexy is sensitive to experimental conditions, and murine cataplexy may occur more frequently when anxiety and physical restrictions are minimized.

## A WORKING DEFINITION OF MURINE CATAPLEXY

The group reached a consensus that the defining features of murine cataplexy are:

1. An abrupt episode of nuchal atonia lasting at least 10 seconds.
2. The mouse is immobile during the episode.
3. Theta activity dominates the EEG during the episode.
4. At least 40 seconds of wakefulness precedes the episode.

In a nutshell, murine cataplexy is a sudden transition from wake into a state physiologically similar to REM sleep. Though this state is not yet well understood, the group expressed confidence that it resembles human cataplexy closely enough that the term "murine cataplexy" is appropriate.

The atonia during cataplexy is the lowest nuchal muscle tone in the EMG recording. Recordings from neck extensor muscles may be most appropriate as loss of axial tone is a common feature of human and murine cataplexy.

To distinguish cataplexy from REM sleep, the definition requires that a mouse be awake for $\geq$ 40 seconds prior to an episode of cataplexy. This sustained wake is a necessary part of the definition because wild type mice can have brief awakenings lasting 10-20 sec in the middle of an extended episode of REM sleep.[51] Fujiki and colleagues have shown that sustained wake lasting $\geq$ 40 sec almost never precedes REM sleep in normal mice, whereas sustained wake often precedes cataplexy in orexin-deficient mice.[51] In addition, episodes of cataplexy defined with this rule are reduced by the tricyclic anti-cataplexy medication desipramine but not by modafinil, thus demonstrating their neurochemical similarity to human cataplexy.[52]

Accurate scoring of murine cataplexy requires EEG and EMG recordings with simultaneous video recordings to document each episode of immobility. The group expressed concern that video recordings alone might not reliably distinguish cataplexy from quiet wake or sudden transitions to NREM sleep and recommends that if researchers use simpler techniques, they use alternative nomenclature. For example, if mouse behavior is scored using video alone, the term "abrupt behavioral arrests" is more appropriate.[42,44] If using just EEG/EMG recordings, behavioral immobility cannot be confirmed, so an episode could be described as a "cataplexy-like state."

This polygraphic and behavioral definition of cataplexy should not be applied to human or canine cataplexy. Human cataplexy is defined as muscle weakness triggered by strong emotions,[53] and this association with emotions is essential for differentiating the weakness of cataplexy from transient weakness of other causes.

Rat models of narcolepsy also have sudden episodes of atonia similar to those seen in mice. Rats expressing a toxic transgene in the orexin neurons have postnatal loss of the orexin neurons and a phenotype much like that seen in mice with the same transgene.[54] These rats have 3-4 episodes each night of sudden atonia with a theta-dominated EEG lasting about 2 minutes.[54] However, these rats also are reported to have some episodes of atonia with a wake-like EEG.[54] A recent study of these rats describes a 75% reduction in CSF orexin concentration and 2-3 episodes/night of abrupt atonia with a REM sleep-like EEG.[55] Lesions of the orexin field in rats produces similar behavior.[56] These episodes of atonia are most common during active wake and are quickly followed by a resumption of activity, but in contrast to narcoleptic mice, the atonia in rats is usually preceded by 20-120 seconds of NREM sleep.[54-56] These events are difficult to study as they are relatively infrequent, and more research is needed to define cataplexy in rat models of narcolepsy.

## LIMITATIONS OF THE DEFINITION

This definition should improve the study of murine cataplexy across labs, but it has several limitations. First, the atonia and EEG theta activity of murine cataplexy are very similar to that seen during REM sleep, so cataplexy is mainly distinguished by the preceding wakefulness. Thus, it remains unknown whether the mouse is conscious as in human cataplexy, or whether these are quick transitions into REM sleep. Second, the definition requires that the mouse is completely immobile, and so it may overlook partial cataplexy. Finally, unlike human sleep scoring, there are no consensus definitions of normal wake and sleep stages in mice. Even the definition of theta activity varies between research groups. We hope that future working groups can develop standard definitions of normal sleep/wake behavior in rodents.

## FUTURE DIRECTIONS

This workshop highlighted many opportunities to improve our understanding of murine cataplexy. Triggering of cataplexy by positive emotions is common in people and dogs with narcolepsy, but recognizing positive emotions in mice is quite challenging. Still, there are hints of an emotional connection: running wheels are rewarding for mice and markedly increase cataplexy[47]; and murine cataplexy may also be increased by anticipation of food or other rewards.[49,57] Even more challenging is establishing whether mice remain conscious during cataplexy, but this could be examined by testing whether behaviorally conditioned mice respond to a stimulus presented during cataplexy once the paralysis ends.

Mice with disrupted orexin signaling also provide an excellent opportunity to study the underlying neurobiology of cataplexy and REM sleep. Are the phasic phenomena of REM sleep (saccadic eye movements, muscle twitches, PGO waves, central apneas) absent during cataplexy? In what ways is murine cataplexy neurochemically distinct from REM sleep? Is cataplexy worsened by conditions that increase REM sleep pressure? Addressing questions such as these will shed light on the neural mechanisms of atonia and how strong positive emotions can trigger cataplexy.

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