Gender differences in narcolepsy: What are recent findings telling us?

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Abstract

Three papers currently published in SLEEP using two different mouse models of narcolepsy, including either *Hcrt-tTa;TetO* diptheria toxin-A (DTA) or Hypocretin knock-out (Hcrt-KO) mice, suggest important gender differences in narcolepsy expression. Specifically, these recent data corroborate previous findings in mice demonstrating that females show more cataplexy events and more total cataplexy expression than males. Moreover, in the neurotoxic DTA mouse model, females show earlier onset of cataplexy expression than males during active Hcrt cell loss. Finally, females show a doubling of cataplexy during estrous compared to other phases of the estrous cycle. These findings are reviewed in the broader context of prior published literature, including reported gender differences in Hcrt expression and hormonal influences on sleep and wakefulness. Although similar findings have not been reported in humans, a systematic evaluation of gender differences in human narcolepsy has yet to be performed. Taken together, these animal data suggest that more research exploring gender differences in human narcolepsy is warranted.

Statement of Significance

Gender differences in human narcolepsy have not been previously explored. However, recent findings from several independent research groups now demonstrate that female narcoleptic mice show more cataplexy events and earlier onset of cataplexy expression than males. Moreover, cataplexy expression varies in females across the estrous cycle. These animal data suggest that more research is needed to explore gender differences in human narcolepsy.

Three papers in *SLEEP* demonstrate gender differences in the phenotypic expression of narcolepsy in mice[1–3], an area of research that has remained greatly understudied. Although narcolepsy as manifested by excessive sleepiness and cataplexy was first described over 140 years ago by Westphal, Gelineau and Fischer[4], a systematic evaluation of gender differences in narcolepsy has not comprehensively been undertaken. Some clinical reports have suggested that cataplexy may be more common in women than men[5,6]. However, conflicting findings on gender and narcolepsy are found in the literature and are likely complicated by gender differences in delivery of medical care. For example, women are reported to be less likely than men to have access to diagnostic sleep testing[7] and there is significantly more years following symptom onset to receive a narcolepsy diagnosis[8,9]. New data from mouse models of narcolepsy published in *SLEEP* suggest important gender differences in cataplexy severity and age of onset, as well as the severity of cataplexy as a function of the estrous cycle.

In this Perspective, we briefly review the findings of these three publications on gender differences in murine narcolepsy while also placing their results in the broader context of prior published literature. However, it is important to first highlight the different methodological approaches employed in these research studies that could result in some inconsistencies in findings across the studies, as well as the interpretation of the results (see Table 1).

Methodological considerations in the three studies

Arthaud and colleagues[3] utilized the traditional hypocretin (orexin) knock-out (Hcrt-KO) mouse model where mice are born without the Hcrt peptide even though Hcrt cells otherwise remain intact. In contrast, Sun et al.[1] and Piilgaard et al.[2] employed a selective Hcrt neurotoxic approach using bigenic *Hcrt-tTa;TetO DTA* mice. The latter approach leads to selective neurodegeneration of Hcrt neurons by induction of a dipheria toxin A (DTA) transgene specifically in Hcrt neurons following removal of doxycycline (DOX) from the animal chow (DOX- condition)[10]. To induce at least a 90% loss of Hcrt neurons, DOX was removed from the chow postnatally for 4 weeks in the Piilgaard study (DOX- condition ending at age 11-15 weeks)[2] and for 6 weeks in the Sun publication[1] (DOX- condition ending at age 20-25 weeks). Although Sun and colleagues[1] performed recordings during the active phase of neuronal loss to identify the timing of onset of cataplexy and related symptoms, the Piilgaard group[2] started recordings only after neuronal loss was essentially complete following the reintroduction of DOX+ chow.

The three studies also differed in housing conditions that may impact cataplexy expression (Table 1). For example, although mice were housed in individual cages, Arthaud and colleagues[3] utilized multiple conditions that included housing males and females either separately in different recording rooms or together in the same recording room. Moreover, this group also recorded both spontaneous cataplexy and food elicited cataplexy using chocolate. The Sun group[1] utilized running wheels in cages, a technique known to significantly increase the likelihood of cataplexy in narcoleptic mice[11]. In contrast, the Piilgaard group[2] housed males and females separately and did not employ either chocolate or running wheels to impact cataplexy.

Although all groups scored cataplexy according to standard consensus criteria[12], there were important differences in scoring and statistical methodology. The Arthaud[3] and Piilgaard[2] groups scored recordings manually using 4-second epochs, whereas the Sun group[1] utilized an automatic scoring system using 10-second epochs (Table 1). Finally, both the Arthaud[3] and Piilgaard[2] groups provide direct statistical comparisons between male and female groups. In contrast, the Sun group[1] provides age of onset and other related data only within each gender, thus rendering direct gender comparisons on other findings more difficult to assess.

Gender-specific differences in phenotypic expression of narcolepsy

Where direct gender comparisons are provided in the three publications (Table 1), female mice appear to exhibit more cataplexy than males with respect to total cataplexy duration and increased cataplexy bout number[2,3], as well as an earlier onset of the first appearance of cataplexy during the period of active Hcrt neuronal cell loss[1]. Moreover, male mice showed a progressive increase in cataplexy bout duration during active Hcrt cell loss, whereas female cataplexy bout durations remained unchanged from first onset to the end of the neurogeneration phase[1]. These latter data indicate that female mice show more severity at onset of the narcolepsy phenotype compared to males.

The Arthaud group also systematically evaluated cataplexy as a function of the estrous cycle in females and demonstrated a doubling of cataplexy during the estrous phase compared to other stages of the cycle[3]. This increase in total cataplexy during estrous was driven by a doubling of cataplexy bout number, whereas cataplexy bout durations did not change across the cycle. Piilgaard and colleagues[2], in contrast, found that cataplexy did not change according to the estrous cycle, but data on only 2 mice are provided in their supplemental material. Thus, this negative finding may be related to an inadequate sample size.

Additionally, the Arthaud group was the only one to house males and females either together or separately in the same recording rooms and found that the presence of an animal of the opposite sex in the same recording room had no effect on vigilance states of either male or female mice. Moreover, the stage of estrous of females housed in the same room as males had no influence on cataplexy. The authors did not directly test, however, whether the mixing males and females in the same cages had an effect.

Importantly, some inconsistencies were noted across studies. For example, although Arthaud et al[3] finds that females show an increase in both cataplexy episode number and mean episode duration, Piilgaard et al[2] show that females have more episodes of cataplexy but shorter mean cataplexy episode durations than males. To what extent the narcolepsy mouse model employed, i.e., the loss of Hcrt peptide (Hcrt-KO model) vs loss of Hcrt neurons (DTA model), may impact this difference is unclear. In contrast, the Sun group[1] found that males and females exhibit similar levels of cataplexy, but they do not provide direct statistical comparisons between groups.

In addition to cataplexy, both research groups employing the DTA neurodegeneration approach also describe similar "delta attacks" or a "delta state" characterized by sudden brief periods of movement cessation with high delta EEG activity but with eyes open, maintenance of posture without loss of muscle tone[1,2]. These delta events were not described in the Hcrt-KO mouse model. The Piilgaard group[2] reports that females show significantly more "delta attacks" than males, including total duration, number of events and event bout durations.

Sleep state instability is a known "biomarker" of narcolepsy with a greater frequency of transitions between states of sleep and wake. Interestingly, state instability was found to differ across the studies according to gender. In mice exhibiting both cataplexy and delta attacks, females show much greater state instability than males with greater frequency of state transitions[2]. However, in the Hcrt-KO mouse model where such "delta attacks" are not reported[3], males show more state instability than females (see Table 1). In the latter study, males showed more episodes of wake, NREM and REM sleep than females but with significantly fewer episodes of cataplexy. Finally, the two studies providing direct comparisons of males vs females show that narcoleptic males show significantly more NREM and REM sleep than females[2,3].

Data on EEG spectral analyses were provided in the two DTA neurodegenerative studies, but only the Piilgaard group[2] employed direct male vs female statistical comparisons. These authors[2] identified a decrease in fast delta activity in NREM sleep, as well as a decrease in theta power in REM sleep, in female mice compared to males. Moreover, they showed that the "delta attacks" are

associated with mixed EEG activity with a delta predominance, but unique in that the EEG activity was less correlated with NREM sleep. Cataplexy events, however, showed a similar theta predominance compared with REM sleep. Taken together, these data indicate that males and females show subtle spectral differences during sleep in narcolepsy and that Hcrt DTA ablated animals may have an additional state resembling a sleep attack but with a unique fingerprint of EEG activity compared to NREM sleep.

Historical perspective and prior literature

The Arthaud et al[3] and Piilgaard et al[2] findings are consistent with a recent study by Coffey et al[13] which first showed that female mice exhibit significantly more cataplexy bouts than males. This earlier study employed the DTA Hcrt-specific neurotoxic mouse model and examined the differences in narcolepsy features as a function of age of onset with respect to Hcrt cell loss in young vs adult mice. Although cataplexy and maintenance of wake were similar independent of age of onset, gender-specific effects on cataplexy were consistent in both age groups. Similarly, narcoleptic dogs, which are known to have a genetic mutation affecting the Hcrt-2 receptor[14], interestingly demonstrate similar findings in that female dogs show an earlier age of cataplexy onset and spend a significantly greater total time in cataplexy than males[15]. However, this gender difference in Dobermans was reported to not be maintained once the dogs reached adulthood[15].

Gender-specific differences in human narcolepsy are less well studied, but some similarities are noteworthy. For example, although men and women appear to have equal risk in developing narcolepsy[5], several studies suggest that the first symptoms of cataplexy or excessive sleepiness appear at an earlier age in women[9,16]. Moreover, a study of 1099 narcolepsy patients as part of the European Narcolepsy Network (EuNN) suggests that the mean sleep latency on the multiple sleep latency test (MSLT) is significantly shorter for women compared to men[9], findings consistent with a later study[8]. A more recent analysis of the EuNN database employed unsupervised machine learning with hierarchical clustering and identified four separate clusters for patients with narcolepsy with cataplexy[17]. One cluster in particular, cluster 4, was found to have a striking female predominance, demonstrating a combination of mild cataplexy, hypnagogic hallucinations and sleep paralysis, prompting the authors to speculate on a female-specific narcolepsy subtype. However, a cluster with more severe cataplexy showing a female predominance was not identified.

Unfortunately, well designed studies examining gender in human narcolepsy expression are lacking and with published results confounded by gender differences in delivery of medical care in

that women are less likely to receive timely diagnostic testing[7]. Complicating such analyses, narcolepsy symptoms, including cataplexy, vary greatly across patients irrespective of gender[4]. To illustrate, one study divided all patients into those with frequency of cataplexy of at least one time per month or less than one time per month[18]. This study suggested that patients who have cataplexy at least one time per month were mainly men yet did not report on gender differences for those with weekly or daily cataplexy. It should not be surprising, then, that published findings on gender have varied considerably from either a slightly higher prevalence in men[9,19] to a considerably higher prevalence in women[6,20].

A fundamental question pertains to the neurobiological basis for a potential gender difference in narcolepsy expression. In this respect, there are considerable data to suggest a number of possible mechanisms based on sex. First, females have higher Hcrt expression in the hypothalamus as measured by pre-pro Hcrt mRNA expression[21] or radioimmunoassay[22], as well as sex differences in the expression of Hcrt receptors in both central and peripheral tissues[23].

Second, sex-dependent hormonal expression and fluctuations across the estrous cycle in females have long been thought to impact sleep-wake expression[24–26]. For example, cycling female rodents show reduced REM sleep expression with increased EEG spindle density when in proestrous and, to a lesser extent in estrous[27,28]. Similarly, an increase in spindle frequency and a small decrease in REM sleep has been described in human women during the luteal phase[29,30]. In contrast, REM latency is shorter in post-ovulatory luteal phase compared to the pre-ovulatory follicular phase in women[30]. Unfortunately, human data on cataplexy expression across the menstrual cycle is completely lacking.

Finally, our own work has shown that cataplexy in mice is favored when the ambient temperature is at the low end of the thermo-neutral zone, whereas cataplexy expression appears to markedly decrease as ambient temperatures approach the high end of thermoneutrality[31]. Given that females have a higher thermal preference than males[32], it remains unclear if ambient temperature may impact the higher cataplexy expression in females. The potential impact of these and other mechanisms require further investigation.

Summary

Considerable evidence now suggests a gender difference in the phenotypic expression of narcolepsy. These data are most consistent in the animal literature where such associations have been systematically investigated. These findings include a more severe form of cataplexy with increased cataplexy bout number and earlier age of onset in females. In contrast to the animal data,

clinical experience has yet to report major effects of gender on human cataplexy severity or characteristics, but systematic analyses of gender-specific effects are lacking. Future research is needed to corroborate these animal findings while also examining potential gender differences in triggers (e.g. sport, emotions, sexual activity) or frequency of partial cataplexy, as well as the potential indirect gender effects of excessive sleepiness which could have a "gating effect" on cataplexy.

Although data for gender-specific differences in human narcolepsy are sparse, sex differences are well described for other sleep disorders. For example, females show a predominance of insomnia and restless legs syndrome, whereas in males there is a higher prevalence for REM sleep behavior disorder (RBD) and Klein Levin Syndrome[33]. The male predominance of obstructive sleep apnea is also well understood, including the tendency for women to show an increase in sleep-disordered breathing after menopause[34]. The role of gender in cataplexy expression in humans, including the association with the menstrual cycle, should be a subject of future investigation.

A remaining question pertains to what is the impact of a gender difference in cataplexy expression for future research and clinical management? Animal research has historically focused on research protocols that only include male mice. However, there is a growing movement in animal neuroscience to include females in research protocols so as to identify important gender effects[35,36]. Most researchers would agree with this assessment. Indeed, Sun et al. suggest that preclinical narcolepsy work should include both male and female mice and argue that their own results suggested only minor sex-specific differences[1]. However, three other studies now demonstrate significant gender differences in mice[2,3,13], including a doubling of cataplexy during estrous in females[3]. These findings are sure to increase variability in recorded cataplexy variables when combining sexes in experimental protocols, potentially driving a need to increase animal numbers to achieve statistical power to identify significant differences when both sexes are combined. Notwithstanding this potential constraint, more research on gender-specific differences in narcolepsy is clearly needed. Such research may also provide new avenues for future diagnostic approaches and influence approaches to therapy.

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Table 1: Summary of methodology and findings from three papers published on gender differences in narcolepsy expression.

	Arthaud et al.[3]	Piilgaard et al.[2]	Sun et al.[1]
Methodology			
Mouse line	Hcrt-KO	DTA	DTA
Scoring of states	Manual (4 s epochs)	Manual (4 s epochs)	Auto (10 s epochs)
Findings			
Cataplexy-related cage environment	Spontaneous & FECT	Spontaneous only	Running wheels
Total Cataplexy	F>M	F>M	F≅M
Number cataplexy episodes	F>M	F>M	F≅M
Cataplexy episode Duration	F>M	M>F	F≅M
Age cataplexy onset	Not evaluated	Not evaluated	F earlier than M
Estrous phase	↑Cataplexy	Inadequate data	Not evaluated
Delta attacks	Not reported	F>M	M vs F not evaluated
Total REM sleep	M>F	M>F	M vs F not evaluated
Total Wake	F=M	F>M	M vs F not evaluated
State instability	M>F	F>M	M vs F not evaluated
NREM delta power	Not evaluated	↓Fast delta in F	M vs F not evaluated
REM theta power	Not evaluated	↓Theta in F	M vs F not evaluated

Abbreviations: Hcrt-KO, Hypocretin/orexin knock-out mice; DTA, *Hcrt-tTa;TetO DTA* mice; FECT, Food Elicited Cataplexy Test.