

# Etiopathogenesis and Neurobiology of Narcolepsy: A Review

SWARUP KUMAR<sup>1</sup>, HARITHA SAGILI<sup>2</sup>

## ABSTRACT

Narcolepsy is a chronic lifelong sleep disorder and it often leaves a debilitating effect on the quality of life of the sufferer. This disorder is characterized by a tetrad of excessive daytime sleepiness, cataplexy (brief loss of muscle tone following strong emotion), hypnagogic hallucinations and sleep paralysis. There are two distinct subgroups of Narcolepsy: Narcolepsy with cataplexy and Narcolepsy without cataplexy. For over 100 years, clinicians have recognised narcolepsy, but only in the last few decades have scientists been able to shed light on the true cause and pathogenesis of narcolepsy. Recent studies have shown that a loss of the hypothalamic neuropeptide Hypocretin/Orexin causes Narcolepsy with cataplexy and that an autoimmune mechanism may be responsible for this loss. Our understanding of the neurophysiologic aspect of narcolepsy has also significantly improved. The basic neural mechanisms behind sleepiness and cataplexy, the two defining symptoms of narcolepsy have started to become clearer. In this review, we have provided a detailed account of the key aspects of etiopathogenesis and neurobiology of narcolepsy, along with a critical appraisal of the more recent and interesting causal associations. We have also looked at the contributions of neuroimaging to the etiopathogenesis of Narcolepsy.

**Keywords:** Narcolepsy, Cataplexy, Hypocretin/ Orexin, Human Leukocyte Antigen (HLA), Rapid eye movement (REM) sleep

## INTRODUCTION

Narcolepsy is a chronic sleep disorder that negatively impacts the quality of life of the sufferer. The usual age of onset is between 15 and 25 years. It is characterized by the classic tetrad of excessive daytime sleepiness, cataplexy defined as brief loss of muscle tone following strong emotion, hypnagogic hallucinations (occurring at sleep onset) and sleep paralysis. The clinical presentation is variable in terms of symptoms and intensity over time. There are two distinct groups of patients, i.e. Narcolepsy with Cataplexy and Narcolepsy without cataplexy.

Our present understanding of the pathogenesis of Narcolepsy is that an autoimmune mediated loss of a specific hypothalamic neuropeptide, Hypocretin causes this disorder. The loss of Hypocretin neurons has been definitely shown in Narcolepsy-Cataplexy [1-4]. Evidence, such as a strong association with HLA (Human leukocyte antigen) DQB1\*06:02, strongly suggest an autoimmune basis for Narcolepsy [5]. Recent studies have also shown an association with a variety of genetic and environmental factors. Further research would be necessary to confirm the autoimmune hypothesis and also address the role of these factors in the pathogenesis of Narcolepsy. Also, a better understanding of the neural pathways behind the symptoms of Narcolepsy will provide us valuable knowledge of the neurobiology of narcolepsy.

## HISTORICAL BACKGROUND OF NARCOLEPSY

Narcolepsy, from the Greek words “narco” and “lepsy” literally means a fit of stupor/stiffness. The terminology was first used by the French physician, Gélinau J in the late nineteenth century in his classical report of a wine cask maker who suffered from the disorder. Interestingly, he could not differentiate the sleep attacks from muscle weakness episodes which were brought about by emotions. The latter was then described as a separate entity by Loëwenfeld as cataplexy.

In the early half of the twentieth century, there was not much focus in research on narcolepsy. Daniels in 1934 firstly emphasized upon

the classic tetrad of excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations which was later defined by Yoss and Daly at the Mayo Clinic [6]. The discovery of REM (Rapid eye movement) sleep in 1953 by Kleitman N and his student Aserinsky E led to primary resurgence in interest for Narcolepsy research.

In the following decade, the association between sleep onset REM periods and narcolepsy was first reported by Vogel et al in their paper, The dream of Narcolepsy. Further studies with EEG analyses on patients recognized narcolepsy as a primary REM sleep dysregulation. The Multiple sleep latency test (MSLT) which objectively evaluates the excessive sleepiness episodes and now a valuable diagnostic tool in Narcolepsy was first described by Carskadon et al., [7].

Further insight into understanding narcolepsy came in the 1980s when an autoimmune causation for narcolepsy was proposed. Honda et al., firstly described the association between narcolepsy and HLA antigens (HLA DR2) [8]. Other investigators then linked further HLA haplotypes such as HLA DQB1\*0602 with narcolepsy [5]. The year 1998 marked a milestone in narcolepsy research with the discovery of the neuropeptide, Hypocretin/ Orexin, the absence of which is now believed to be responsible for most of the symptoms of Narcolepsy [1]. In the following years, several studies had shown compelling evidence that Narcolepsy can be caused by a loss in orexin/hypocretin signalling as demonstrated by a lack of Hypocretin in the hypothalamus and CSF of narcolepsy patients [2,3]. Many investigators then speculated an autoimmune mechanism for the disorder, which has been supported by several studies .

## EPIDEMIOLOGY

The prevalence of narcolepsy is reported to be in the range of .02 to .067 % in North American, Western European and Asian populations [9]. However, two Japanese studies reported clearly higher prevalence rates of 0.16 and 0.18 % respectively. Whether these observations reflect a particularity of the Japanese population or a bias in the methodology of the two studies (as the two studies

did not require polysomnography to verify the diagnosis) remained to be investigated. It has now been suggested that the differences in prevalence may partly be related to the association between narcolepsy and the prevalence of HLA DQB1\*0602 phenotype [10]. Epidemiological studies have most often been performed for narcolepsy with cataplexy as the other symptoms are poorly defined to be useful in epidemiology. Further, the high prevalence rates for sleep paralysis (6.2%) and hypnagogic hallucinations (24.1%) in the general population indicate that these symptoms are not specific to narcolepsy. For Narcolepsy without Cataplexy; studies have shown that this subgroup represents approximately 10-50% of all narcolepsy cases [5].

The incidence rates for Narcolepsy with or without Cataplexy are 1.37 per 100,000 population per year and for Narcolepsy with Cataplexy, 0.74 per 100,000 population per year in the USA [9]. The incidence rate is highest in the second decade and the disorder is more common in men [9].

Although there may be variations in incidence and prevalence rates among various ethnic populations, there is a striking similarity in clinical presentation and natural history of narcolepsy-cataplexy across patients of various ethnic groups and cultural backgrounds. Onset of narcolepsy is typically in adolescence with average age at onset between 15 and 30 years [11]. However, in rare occasions, the age at onset of symptoms can be as late as 40 yrs of age. There is also a significant delay in the diagnosis of narcolepsy of an average of 16-22 years from the onset of symptoms suggesting that not all cases diagnosed after the age of 30 years are due to late onset of symptoms. This delay in diagnosis is especially pronounced when cataplexy is absent initially.

Preliminary studies have shown an increased association of narcolepsy with the timing of birth more frequently in the month of March termed the "March birth Effect" [12]. The risk for narcolepsy with clear-cut cataplexy is apparently more than doubled by a March birth suggesting that environmental factors during the prenatal or neonatal period are etiologically significant factors [12].

An interesting observation of note is that while the HLA Haplotype DQB1\*0602 confers strong susceptibility to narcolepsy; there is a dominant protection against type I diabetes. Siebold et al., noted a previously unrecognized interplay between the peptide pockets in the crystal structure, which implies that subtle changes in the presentation of the peptide can either confer protection against Diabetes Type 1 or susceptibility to narcolepsy [13].

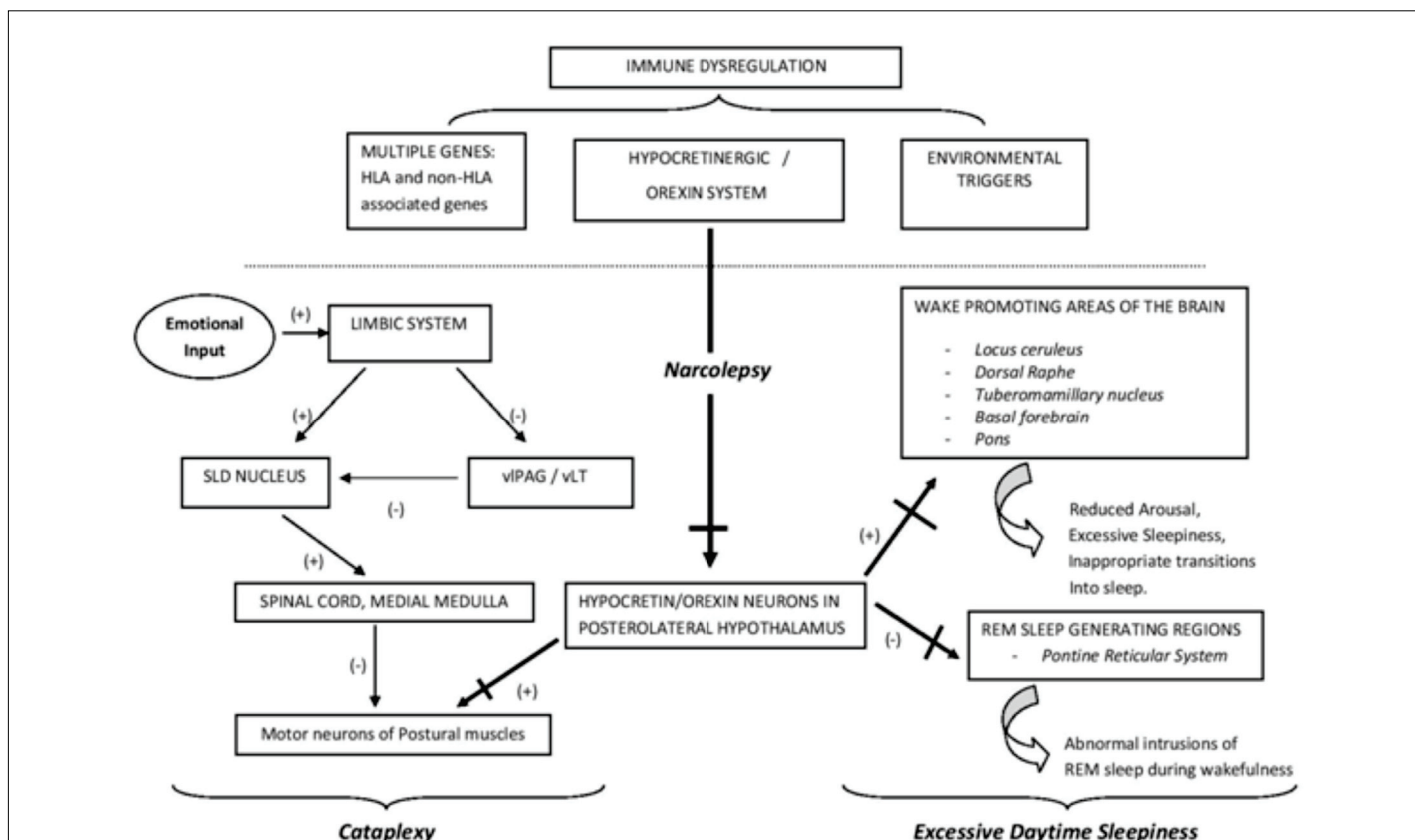
## ETIOPATHOGENESIS

Current evidence on the pathogenesis of narcolepsy comes from much of studies being focused on narcolepsy with cataplexy with pointers towards both genetic and environmental factors.

## GENETIC FACTORS

The genetic aspects of narcolepsy are complex. Changes in several genes have been identified that influence the risk of developing narcolepsy, though it is unclear how these influence the risk of developing the condition. The best described genetic change is the HLA DQB1 gene which is part of the Human Leukocyte Antigen (HLA) complex [5]. This gene encodes a protein that plays a vital role in antigen presentation (peptides) to the immune system. Other HLA genes that are associated with narcolepsy include HLA DRB1 and HLA DQA1 [14]. The HLA alleles play a primary role in disease predisposition [Table/Fig-1].

Although most cases of narcolepsy are sporadic, there are definite cases with familial clustering. The risk of narcolepsy in first degree relatives of patients is 10-40 times higher than in the general population [15]. It is also observed that multiplex families are more frequently HLA DQB1 negative than sporadic cases, suggesting the importance of non HLA genetic factors. Non HLA genes that have studied in narcolepsy are CPT1B (carnitine palmitoyltransferase 1B), CHKB (choline kinase beta), TNF (Tumor necrosis factor) and TNFRSF1B (TNF receptor super family member 1B), all of which are thought to play a role in immune system function. Resistance to narcolepsy is associated with minor alleles of a SNP (single nucleotide polymorphism) and



**[Table/Fig-1]:** A diagrammatic model summarizing the Etiopathogenesis and Neurobiology of Narcolepsy., Key: SLD nucleus – Sublaterodorsal nucleus; vPAG – Ventrolateral Periaqueductal Gray; vLT- Lateral Tegmentum of Pons; (+) → Excitatory signal; (-) → Inhibitory signal; (+) → Loss of Excitatory signal; (-) → Loss of Inhibitory signal

a marker in the NLC1A (Narcolepsy candidate 1A) gene (610259) on chromosome 21q22.

## HLA HAPLOTYPE

Human Leukocyte antigens (HLA) are linked to many autoimmune diseases, and narcolepsy has the strongest known HLA association. A variation of the HLA-DQB1 gene called HLA-DQB1\*0602 has been found to have a primary association with narcolepsy, particularly in patients of narcolepsy with cataplexy [5]. A 200 fold risk of developing narcolepsy exists in simply carrying this gene. More than 85% of patients having narcolepsy with cataplexy have HLA DQB1\*0602, often in combination with HLA DRB1\*1501, while only around 40 % of the patients having narcolepsy without cataplexy have HLA DQB1\*0602 suggesting increased heterogeneity in narcolepsy without cataplexy [16]. Though the association of HLA DQB1 with narcolepsy is more specific, its usefulness as a screening or diagnostic test is limited by the fact that it has a high prevalence (as high as 12%-38%) in the general population, and that its sensitivity is highest in patients of narcolepsy with cataplexy, a group in which additional diagnosis is rarely necessary [17].

## HYPOCRETINS

Hypocretins, also called orexins, are dorsolateral hypothalamic neuromodulators that function in regulating sleep-wake cycles, food intake, and pleasure-seeking behaviour. Two Hypocretins have been discovered and they are named Hypocretin (HCRT) 1 and 2 or Orexin (ORX) A and B respectively. Both Hypocretins are amino acid peptides with HCRT 1 (Hypocretin 1) having disulfide bridges and HCRT 2 (Hypocretin 2) shows a 46% amino acid identity with that of HCRT 1 [18]. The coding gene for Hypocretins i.e. HCRT (Hypocretin neuropeptide precursor gene) is located in chromosome 17q21-q24. The corresponding receptors for Hypocretins i.e. HCRTR 1 (Hypocretin receptor 1) and HCRTR 2 (Hypocretin receptor 2) have also been described [18]. Deficiency of hypocretin leads to abnormalities of these systems including maintaining wakefulness and regulating transitions between sleep and wake. While it is evident that loss of function mutations in the HCRT gene should cause narcolepsy, it is to be noted that such mutations are rare in cases of human narcolepsy and the loss of hypocretin neurons is thought to be by a different mechanism possibly an immunological response [1,3,19].

Several studies have shown that a loss of hypocretin neurons definitely causes Narcolepsy with cataplexy [1-4]. The evidence for Hypocretin deficiency in narcolepsy is as follows.

The first link that hypocretin deficiency could be associated with narcolepsy was from the study by Foutz et al., who showed an autosomal recessive pattern of inheritance in Doberman Pinschers [20]. This was later identified as a mutation in the hypocretin (orexin) receptor 2 gene by Lin et al., [21].

One of the key reports of Hypocretin deficiency in Narcolepsy-Cataplexy came from the study by Nishino et al., [1]. Their study was a case-control study in which 7 of 9 patients having narcolepsy with cataplexy had no detectable hypocretin, with the neuropeptides being detectable in all their matched controls. Studies by Peyron et al., and Thannikal et al., have strongly supported this hypocretin neuro transmission deficiency in narcolepsy with cataplexy [2,3]. Another study by Thannikal et al., showed that this loss of hypocretin neurons is highly selective as the neurons producing the Melanin concentrating hormone (MCH) which are intermingled with the orexin neurons seemed to be completely unaffected. Also, the reduction in number of hypocretin neurons is around 85% to 95% with evidence of gliosis suggesting an inflammatory nature of the disease [19].

Approximately 90% of patients of narcolepsy with cataplexy have low CSF (Cerebrospinal fluid) hypocretin levels while only 10% to 20% of patients classified as having narcolepsy without cataplexy

show low CSF Hypocretin levels. It is thought that simply a less severe injury to the orexin neurons occurs resulting in small reduction in Hypocretin levels in patients of narcolepsy without cataplexy [2].

The clinical importance of measuring CSF Hypocretin levels in these two categories of narcoleptic patients is limited by the lack of association between low Hypocretin levels and Narcolepsy without cataplexy and also the fact that Narcolepsy with cataplexy is a group in which additional diagnosis rarely necessary. Nevertheless, the primary utility of measuring CSF Hypocretin levels remains in evaluating patients with equivocal cataplexy and equivocal neurophysiologic testing [22].

## AUTOIMMUNE HYPOTHESIS

The combination of HLA antigens, hypocretin neuron loss and hypocretin deficiency and onset in the second decade of life strongly points towards an autoimmune etiology. Given that genetic susceptibility to narcolepsy is linked to a specific HLA type; many investigators have suspected an immunologic basis for the disease, either by an autoimmune mechanism or in response to external antigens [23].

Several observations lend strong support to the autoimmune hypothesis [24-31]. Some of these are outlined below.

In a study by Cvetkovic-Lopes et al., Enzyme-linked immunosorbent analysis (ELISA) was used to show that sera from patients having narcolepsy with cataplexy had higher Tribbles Homolog 2 transcript (Trib2)-specific antibody titers compared with those in normal controls [24]. This finding was replicated in another study by Kawashima et al., which raises the possibility that some patients of narcolepsy could be suffering from anti-Trib2 autoimmune disorder [27].

A study by Hallmayer et al., has found an association between narcolepsy-cataplexy and polymorphism in the T cell receptor alpha genetic locus that may alter the immune response to some antigens [25].

Other studies have demonstrated associations between levels of interleukin-6, tumor necrosis factor, tumor necrosis factor alpha receptor and narcolepsy [25,26]. However, Fontana et al., have suggested that immune mediated destruction of hypocretin neurons might occur independent of T cells [32].

A case-control study by Smith AJ et al., identified functional auto antibodies in immunoglobulin G fraction of patients with narcolepsy but not controls [28]. They concluded that patients with narcolepsy-cataplexy have a functional IgG autoantibody that enhances postganglionic cholinergic neurotransmission.

A recent study by Kornum et al., identified the possible role of a purinergic receptor gene, P2Y11 as an important regulator of immune-cell survival with implication in narcolepsy [29].

Watson et al have found that higher birth order was associated with an increased risk of developing narcolepsy in people positive for HLA-DQB1\*0602 [30]. This study suggests that immune responses to early childhood infections can predispose to disease development and supports an auto immune etiology for Narcolepsy.

An observed increase in incidence of Narcolepsy following H1N1 influenza vaccine in several studies and countries also lends credible evidence towards autoimmune basis for the disorder [31].

Despite the body of evidence clearly implicating the immune system, future studies will be required to confirm the autoimmune basis of narcolepsy as no key target antigen or humoral/cellular mechanism of immunity that could attack the hypocretin neurons has been identified [33].

## ENVIRONMENTAL CAUSATIONS

The nature of possible environmental triggers in narcolepsy is largely unknown. However studies have shown an association with streptococcal infection, seasonal influenza, and more recently

pandemic A/H1N1 2009 influenza vaccination [22,34-39]. An association between insecticides, weed killers and exposure to heavy metals with narcolepsy has also been recently described [39].

The recent study by Aran et al., addressed the role of streptococcal infections in the aetiology of narcolepsy. They found elevated levels of anti-streptococcal antibodies in patients with recent narcolepsy onset [34]. Streptococcal disease has long been associated with brain dysfunction thought to be based on an immunologic response, such as with Sydenham chorea and, more recently, pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS) [35].

A study by Han et al., described a strong correlation between narcolepsy onset in children and seasonal patterns of upper airway infections, especially following the H1N1 influenza pandemic of 2009 [36].

Following case reports from Finland and Sweden on children and adolescents developing narcolepsy post pandemic H1N1 flu vaccination, investigators started researching for possible role of the vaccine as a trigger for narcolepsy in other ethnic populations. One study by Miller et al., in England found that increased risk of onset of narcolepsy in children and young people after the AS03 adjuvant pandemic vaccine (PandemrixR) was not confined to Scandinavian populations and the magnitude of risk was similar [37]. Results from further studies in other European countries were tabled in the VAESCO report of the ECDC (European centre for disease prevention and control) confirming strong associations between pandemic A/H1N1 vaccine and narcolepsy [38]. However, the CDC reviewed the data from their VAERS (Vaccine adverse effect Reporting system) and found no indication of any association between U.S.-licensed H1N1 or seasonal influenza vaccine and narcolepsy. Further studies are needed to study the association between adjuvant H1N1 monovalent vaccine and narcolepsy.

Other neurological insults that have been linked to narcolepsy include, but are not limited to head trauma, stroke and changes in sleep-wake cycle [39]. All this could affect the levels of hypocretin either transiently or permanently [22].

## ASSOCIATED DISEASES

Individuals affected with Narcolepsy represent a vulnerable segment of the population. Complicating this illness are several sleep as well as general medical comorbidities, of which our understanding is only fractional.

Several recent studies have demonstrated the association of Narcolepsy with other sleep disorders especially sleep apnoea syndrome, REM sleep behaviour disorder and periodic limb movement disorder [40-43]. However, the association with other sleep disorders seems to only have an overall limited effect on the clinical manifestations of narcolepsy [40]. Also, the pathophysiology of these sleep disorders differs from narcolepsy in that they chiefly disrupt nocturnal sleep to bring about clinical manifestations.

Nevsimalova et al showed that sleep apnoea syndrome is frequently associated with Narcolepsy. In this study, they also noted that sleep co morbidities including sleep apnea occur more frequently in Narcolepsy-Cataplexy patients than in Narcolepsy without Cataplexy. Fourty Studies by Nightingale et al., and Wierzbicka et al., have reported high incidence of REM sleep behaviour disorder in patients of Narcolepsy [41,42]. A significant number of patients with cataplexic attacks in these studies also had REM behaviour disorder suggesting a common pathophysiologic background for these two symptoms [42]. Dauvilliers et al., in have demonstrated a high frequency of periodic limb movements during sleep as well as wakefulness in narcoleptic patients [43].

An association between narcolepsy and obesity has been described since the 1970s when case control studies showed that narcoleptic patients eat more snacks than controls, and documented an increase in calorie intake. Several early studies also concluded

that narcoleptic patients have an increased Body Mass index (BMI) [44,45]. Okun ML et al., have also showed that narcoleptic patients have slightly but significantly elevated body mass index relative to matched controls [46]. All of these studies had looked at Narcoleptic patients with cataplexy. Sonka et al., have shown that unlike Narcolepsy-Cataplexy, patients having Narcolepsy without cataplexy neither have an increased BMI nor have a higher incidence of obesity than the general population [47].

Given the considerations about obesity, patients with narcolepsy-cataplexy may be at greater risk than the general population for conditions that can complicate abdominal obesity, including type 2 diabetes mellitus and cardiovascular disease.

## NEUROBIOLOGICAL ASPECTS OF NARCOLEPSY

### Animal Models

The identification of narcolepsy in animals can be traced back to the 1970s when it was first reported in a dash hound and a poodle. Subsequently autosomal recessive inheritance of narcolepsy in canines was discovered and the target canine narcolepsy gene was identified as Hypocretin receptor 2 (HCRTR2) gene [20,21]. It is also interesting to note that unlike in humans, canine narcolepsy is not linked to the Dog Leukocyte Antigen (DLA).

Animal models of human narcolepsy consist of either modification in Hypocretin/Orexin receptors or absence of these peptides.

There are two reliable animal models of human narcolepsy. The first is the narcoleptic canine model in which a mutation in the HCRT 2 gene underlies the narcoleptic symptoms [21]. As in human narcolepsy, the mutation causes a fragmentation of the vigilance states resulting in excessive daytime sleepiness and severe cataplexy elicited by social interaction and palatable food. The second model is in HCRT knockout mice which display a narcolepsy like phenotype. Fragmented sleep and behavioural arrests similar to cataplexy in human narcoleptics occur [48].

Both these animal models have good face validity (ability to demonstrate excessive sleepiness and cataplexy), predictive validity (drugs for human narcolepsy reduce symptoms in animal models) and construct validity (lack of a functional orexin system) [33]. The availability of validated animal models has now enabled researchers to fully understand the fundamental aspects of narcolepsy including its neurobiology.

## NEUROBIOLOGY OF SLEEPINESS

Excessive daytime sleepiness is a defining feature of narcolepsy which is characterized by multiple intrusions of Rapid eye movement (REM) sleep onto wakefulness thereby disrupting the entire sleep architecture. Several possible explanations have been put forth to explain this debilitating symptom. To understand this, we need to know the anatomic and physiological functions of the Hypocretin/orexin (Hcrt/Orx) neurons.

The Hcrt/Orx neuropeptides have been implicated in the control of the sleep-wakefulness cycle and control of REM sleep generation. Majority of the Hypocretinergic neurons are present in the posterolateral hypothalamus. These neurons innervate and excite many of the key wake-promoting systems, including noradrenergic neurons of the locus ceruleus, serotonergic neurons of the dorsal raphe, histaminergic neurons of the tuberomammillary nucleus and cholinergic neurons in the basal forebrain and pons. In relation with the control of REM (Rapid eye movement) sleep generation, Hcrt/Orx projections and receptors have been identified in cholinceptive areas of the pontine reticular formation involved in REM sleep generation demonstrating an inhibitory effect on REM sleep generation.

The loss of Hcrt/Orx signalling in narcolepsy would impair these actions and could remove the inhibiting actions on REM generation

in these pontine regions during wakefulness; consequently, patients would fall directly into REM while still in a wakefulness period. Also, the wake promoting neurons may not receive adequate excitatory drive in the absence of orexins, leading to reduced arousal, disinhibition of sleep promoting pathways and inappropriate transitions in to sleep [18].

This hypothesis could best explain the frequent transitions between wakefulness and sleep, REM sleep fragmentation and excessive sleepiness present in narcoleptic patients [18].

Another possible explanation for excessive sleepiness is that narcoleptic patients can have a higher sleep drive than normal [33]. Research studies have shown that Hypocretin/Orexin neurons in rats and humans were recently shown to be directly innervated by neurons of the suprachiasmatic nucleus, a structure that is responsible for regulation of circadian processes. Thus, a loss of hypocretin neurons would lead to disruption of the circadian sleep/wake control. However this explanation is not plausible as other studies have shown that the total amount of sleep in mice and humans with narcolepsy remains the same as are their responses to sleep deprivation. A study by Mochizuki et al., has also shown that the fundamental circadian rhythms of mice and humans with narcolepsy are close to normal [49].

## NEUROBIOLOGY OF CATAPLEXY

Cataplexy is brief episodes of muscle weakness often triggered by strong emotions. The loss of muscle tone could be partial affecting just the face and the neck or complete resulting in postural collapse. However consciousness is fully preserved during cataplexy. Genuine episodes of cataplexy are triggered by very specific emotions, the most reliable being joking, laughter and anger.

When an individual is in REM sleep, there is loss of tone in the postural muscles of the body. This is termed as REM sleep atonia. The motor neurons are inhibited by GABAergic and Glycinergic pathways from the spinal cord and medial medulla [50]. These inhibitory pathways are in turn activated by Glutaminergic signals from the sublaterodorsal (SLD) nucleus [51]. During wakefulness these neurons are kept in check by the GABAergic neurons from the ventrolateral periaqueductal gray and the lateral pontine tegmentum (vlPAG/vLT) [51]. In cataplexy, the neurons from the vlPAG/vLT are inhibited, thereby disinhibiting the atonia producing pathways resulting in loss of postural tone [52]. How strong emotions can trigger cataplexy is explained by observation of excitatory limbic projections to the SLD and inhibitory limbic projections to the vlPAG/vLT.

Hypocretin/Orexin neurons may be also involved in triggering cataplexy. A study by Yamuy J et al., has shown that hypocretinergic neurons also project to the motor neurons and have an excitatory effect on them [53]. It is possible that a loss of hypocretinergic neurons could lead to atonia. However, the finer details of neural pathways that regulate sleepiness and cataplexy remain to be sorted out.

## NEUROIMAGING IN NARCOLEPSY

Modern neuroimaging techniques offer a non-invasive diagnostic approach to evaluate normal physiological functions as well as pathological processes in sleep disorders.

The key neuroimaging findings in Narcolepsy are outlined as follows.

1. Structural imaging studies using MRI (Magnetic resonance imaging) and MRI based techniques such as VBM (Voxel based morphometry), DTI (diffusion tensor imaging) etc showed localised decreases in grey matter in the brain of narcoleptic patients. The most consistent decrease was in the hypothalamus. This is in concordance with the hypocretin deficit in Narcolepsy-Cataplexy. Additionally, decreases were observed in the nucleus accumbens, frontotemporal cortices and thalamus; all of which represent key projection sites of hypocretinergic neurons [54].

2. Functional imaging studies on the regional brain activity patterns of narcoleptic patients during resting wake state have also indicated a dysfunction of the hypothalamus and multiple cortical areas, paralleling changes demonstrated by structural imaging [55]. These brain changes might relate to specific cognitive and mood disturbances encountered in narcolepsy-cataplexy.
3. Recent studies have also looked at the neural bases behind emotion triggered cataplexy. The disruption of emotional processing in narcoleptic patients with cataplexy has been attributed to altered neural responses in the hypothalamus and the limbic structures in the brain, chiefly the amygdala. However, the evidence for this is sparse. A few fMRI (functional MRI) based studies have evaluated brain responses to both positive and negative stimulations in patients and have found altered amygdalar responses in patients. A study by Brabec et al., has shown decreased amygdalar volume in Narcolepsy-Cataplexy patients which corroborates with the reports from functional imaging studies [56]. It is now thought that the amygdala might play a central role in the neural mechanisms behind cataplexy, possibly through a dysfunctional interaction with hypothalamic and other limbic system regions. Further studies would therefore be needed to better understand the neural correlates of cataplexy.

## CONCLUSION AND FUTURE DIRECTIONS

As our understanding of the pathogenesis of Narcolepsy continues to advance, it is increasingly evident to us that an autoimmune loss of hypocretin neurons is the main cause of Narcolepsy with cataplexy. However, more information would be necessary to completely understand the autoimmune process and also as to how this process can be altered for therapeutic benefits. Further research is also needed to clarify the wide range of genetic factors that may cause narcolepsy and also, other neuropeptides that may be involved in the pathogenesis of narcolepsy.

The discovery of the Hypocretin/Orexin system had brought about a huge surge in research on Narcolepsy that it significantly improved our understanding of this debilitating disorder. Yet more important and basic questions remain to be answered. Which Hypocretin projections are essential for sleep control; How the Hypocretin system is regulated and how cataplexy is linked with hypocretin loss are some of the issues that need to be addressed. Also the development of a working model to explain the neural connections involved in regulating sleepiness and cataplexy would be needed for thorough understanding of narcolepsy. Few imaging studies have investigated the role of limbic pathways in regulating cataplexy. Also, the neural mechanisms behind other symptoms of Narcolepsy such as hypnagogic hallucinations and sleep attacks remain to be studied as no recent neuroimaging studies have been dedicated in assessing the sleeping brain in Narcolepsy.

The relationship between feeding regulation, energy metabolism, emotional affect and narcolepsy needs to be explored. The association between eating disorders and narcolepsy has also been described recently. The findings represented a change in eating behaviour resulting in an increased BMI in narcoleptic patients rather than just an increase in calorie intake.

Finally, the pathophysiology of narcolepsy without cataplexy remains a vastly unstudied field. A detailed understanding of the neural pathways involved in maintenance of the sleep-wake cycle would perhaps shed light on this disorder.

Much stride in research on Narcolepsy has been recently taken that an accurate analysis of the pathogenesis of this disorder may be likely in the near future. This will eventually lead to the formulation of new therapies and may even lead to a cure for Narcolepsy.

## REFERENCES

- [1] Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (Orexin) deficiency in human narcolepsy. *Lancet*. 2000; 355(9197): 39-40

- [2] Thannickal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*. 2000;27(3):469-74.
- [3] Peyron C, Faraco J, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med*. 2000;6(9):991-97.
- [4] Hong SC, Lin L, Jeong JH, et al. A study of the diagnostic utility of HLA typing, CSF hypocretin-1 measurements, and MSLT testing for the diagnosis of narcolepsy in 163 Korean patients with unexplained excessive daytime sleepiness. *Sleep*. 2006; 29(11):1429-38.
- [5] Mignot E, Hayduk R, Black J, Grumet FC, Guilleminault C. HLA DQB1\*0602 is associated with cataplexy in 509 narcoleptic patients. *Sleep*. 1997; Nov;20(11):1012-20.
- [6] Yoss RE, Daly DD. Criteria for the diagnosis of the narcoleptic syndrome. *Proc Staff Meeting Mayo Clinic*. 1957; 32: 320-28.
- [7] Richardson GS, Carskadon MA, Flagg W, van den Hoed J, Dement WC, Mitler MM. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. *Electroencephalogr. Clin. Neurophysiol*. 1978; 45: 621-27.
- [8] Honda Y, Asake A, Tanaka Y, Juji T. Discrimination of narcolepsy by using genetic markers and HLA. *Sleep Res*. 1983; 1(2): 254.
- [9] Silber MH, Krahn LE, Olson EJ, Pankratz VS. The epidemiology of narcolepsy in Olmsted County, Minnesota: A population-based study. *Sleep*. 2002; 25(2):197-202.
- [10] Heier MS, Esviukova T, Wilson J, Abdelnoor M, Hublin C, Ervik S. Prevalence of narcolepsy with cataplexy in Norway. *Acta Neurol Scand*. 2009;120(4):276-80.
- [11] Overeem S, Mignot E, van Dijk JG, Lammers GJ. Narcolepsy: clinical features, new pathophysiological insights, and future perspectives. *J Clin Neurophysiol*. 2001; 18: 78-105.
- [12] Picchioni D, Mignot EJ, Harsh JR. The month-of-birth pattern in narcolepsy is moderated by cataplexy severity and may be independent of HLA-DQB1\*0602. *Sleep*. 2004; 27(8):1471-5.
- [13] Siebold C, Hansen B E, Weyer J R Harlos K, Esnouf R E, Svejgaard, A. et al. Crystal structure of HLA-DQ0602 that protects against type 1 diabetes and confers strong susceptibility to narcolepsy. *Proc Nat Acad Sci*. 2004; 101.
- [14] Mignot E, Lin X, Arrighoni J, et al. DQB1\*0602 and DQA1\*0102 (DQ1) are better markers than DR2 for narcolepsy in Caucasian and black Americans. *Sleep*. 1994; 17: S6-S7.
- [15] Billiard M, Pasquie-Magnetto V, Heckman M, et al. Family studies in narcolepsy. *Sleep*. 1994; 17: S54-S59.
- [16] Tafti M. Genetic aspects of normal and disturbed sleep. *Sleep Med*. 2009; 10 (Suppl 1): S17-S21.
- [17] Peacock J, Benca RM. Narcolepsy: Clinical features, co-morbidities and treatment. *Indian J Med Res*. 2010;131:338-49.
- [18] Nuñez ML, Rodrigo-Angulol, De Andrés, Garzón M. Hypocretin/orexin neuropeptides: participation in the control of sleep-wakefulness cycle and energy homeostasis. *Curr Neuropharmacol*. 2009; 7(1): 50-59.
- [19] Thannickal TC, Nienhuis R, Siegel JM. Localized loss of hypocretin (orexin) cells in narcolepsy without cataplexy. *Sleep*. 2009; 32:993-8.
- [20] Foutz AS, Mitler MM, Cavalli-Sforza LL, Dement WC. Genetic factors in canine narcolepsy. *Sleep*. 1979; 1(4): 413-21.
- [21] Lin L, Faraco J, Li R, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (Orexin) receptor 2 gene. *Cell*. 1999; 98:365-76.
- [22] Bourgin P, Zeitler JM, Mignot E. Review: CSF hypocretin-1 assessment in sleep and neurological disorders. *Lancet Neurol*. 2008; 7(7):649-62.
- [23] Nepom GT. MHC and autoimmune diseases. In: Bach J-F, ed. *Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases*. New York: Marcel Dekker; 1993:143-64.
- [24] Cvetkovic-Lopes V, Bayer L, Dorsaz S, et al. Elevated tribbles homolog 2-specific antibody levels in narcolepsy patients. *J Clin Invest*. 2010; 120(3):713-19.
- [25] Hallmayer J, Faraco J, Lin L, et al. Narcolepsy is strongly associated with the T-cell receptor alpha locus. *Nat Genet*. 2009; 41(6):708-11.
- [26] Himmerich H, Beiting PA, Fulda S, et al. Plasma levels of tumornecrosisfactor alpha and soluble tumor necrosis factor receptors in patients with narcolepsy. *Arch Intern Med*. 2006; 166(16):1739-43.
- [27] Kawashima M, Lin L, Tanaka S, Jennum P, Knudsen S, Nevsimalova S, et al. Anti-Tribbles homolog 2 (TRIB2) autoantibodies in narcolepsy are associated with recent onset of cataplexy. *Sleep*. 2010; 33:869-74.
- [28] Smith AJ, Jackson MW, Neufing P, McEvoy RD, Gordon TP. Afunctional autoantibody in narcolepsy. *Lancet*. 2004;364:2122-4.
- [29] Kornum BR, Kawaswhima M, Faraco J, et al. Common variants in P2RY11 are associated with narcolepsy. *Nat Genet*. 2011; 43(10):1040.
- [30] Watson NF, Ton TG, Koepsell TD, Longstreth WT Jr. Birth order and narcolepsy risk among genetically susceptible individuals: a population-based case-control study. *Sleep Med*. 2012; 13(3): 310-3.
- [31] Wijnans L, et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A (H1N1) pdm09 pandemic and vaccination campaigns. *Vaccine*. 2012; 31: 1246-54
- [32] Fontana A, Gast H, Reith W, Recher M, Birchler T, Bassetti CL. Narcolepsy: Autoimmunity, effector T cell activation due to infection, or T cell independent, major histocompatibility complex class II induced neuronal loss? *Brain*. 2010; 133(Pt 5): 1300-11.
- [33] Burgess CR, Scammell TE. Narcolepsy: Neural mechanisms of sleepiness and cataplexy. *J Neurosci*. 2012; 32(36): 12305-311
- [34] Aran A, Lin L, Nevsimalova S, et al. Elevated anti-streptococcal antibodies in patients with recent narcolepsy onset. *Sleep*. 2009;32:979-83.
- [35] Dale RC. Post-streptococcal autoimmune disorders of the central nervous system. *Dev Med Child Neurol*. 2005; 47: 785-91.
- [36] Han F, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Ann Neurol*. 2011; 70: 410-17
- [37] Miller E, Andrews N, Stellitano L, Stowe J, Winstone AM, Shneerson J, Verity C. Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: Retrospective analysis. *BMJ (Online)*. 2013; 346 (7897), art. no. f794.
- [38] ECDC technical report, 2013. Narcolepsy in association with pandemic influenza vaccination: A multi-country European epidemiological investigation.
- [39] Ton TG, Longstreth WT Jr, Koepsell TD. Environmental toxins and risk of narcolepsy among people with HLA DQB1\*0602. *Environ Res*. 2010;110(6):565-70.
- [40] Nevsimalova S, et al. Narcolepsy: clinical differences and association with other sleep disorders in different age groups. *J Neurol*. 2012; 260: 767-75.
- [41] Nightingale S, Orgill JC, Ebrahim IO, de Lacy SF, Agrawal S, Williams AJ. The association between narcolepsy and REM behaviour disorder (RBD). *Sleep Med*. 2005; 6(3): 253-8.
- [42] Wierzbicka A, Wichniak A, Waliniowska E, Czasak K, Musi Ska I, Szatkowska E, et al. REM sleep behaviour disorder in narcolepsy. *Neural Neurochir Pol*. 2009; 43(5): 421-7.
- [43] Dauvilliers Y, Pennestri MH, Petit D, Dang-Vu T, Lavigne G, Montplaisir J. Periodic leg movements during sleep and wakefulness in narcolepsy. *J Sleep Res*. 2007; 16(3): 333-9.
- [44] Honda Y, Doi Y, Ninomiya R, Ninomiya C. Increased frequency of non-insulin-dependent diabetes mellitus among narcoleptic patients. *Sleep*. 1986;9:254-9.
- [45] Schuld A, Hebebrand J, Geller F, Pollmacher T. Increased body mass index in patients with narcolepsy. *Lancet*. 2000;355:1274-5.
- [46] Okun ML, Lin L, Pelin Z, Hong S, Mignot E. Clinical aspects of narcolepsy-cataplexy across ethnic groups. *Sleep*. 2002 Feb 1;25(1):27-35.
- [47] Sonka K, Kemlink D, Busková J, Pretl M, Srtková Z, Maurovich Horvat E, et al. Obesity accompanies narcolepsy with cataplexy but not narcolepsy without cataplexy. *Neuro Endocrinol Lett*. 2010; 31(5):631-4.
- [48] Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell*. 1999; 98(4): 437-51.
- [49] Mochizuki T, Crocker A, McCormack S, Yanagisawa M, Sakurai T, Scammell TE. Behavioral state instability in orexin knock-out mice. *J Neurosci*. 2004; 24: 6291-6300.
- [50] Soja PJ, Morales FR, Baranyi A, Chase MH. Effect of inhibitory amino acid antagonists on IPSPs induced in lumbar motoneurons upon stimulation of the nucleus reticularis gigantocellularis during active sleep. *Brain Res*. 1987; 423: 353-58.
- [51] Boissard R, Gervasoni D, Schmidt MH, Barbagli B, Fort P, Luppi PH. The rat pontomedullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. *Eur J Neurosci*. 2002;16:1959-73.
- [52] Wu MF, John J, Boehmer LN, Yau D, Nguyen GB, Siegel JM. Activity of dorsal raphe cells across the sleep-waking cycle and during cataplexy in narcoleptic dogs. *J Physiol*. 2004 Jan 1; 554(Pt 1): 202-15.
- [53] Yamuy J, Fung SJ, Xi M, Chase MH. Hypocretinergic control of spinal cord motoneurons. *J Neurosci*. 2004 Jun 9; 24(23):5336-45.
- [54] Kim SJ, Lyoo IK, Lee YS, Lee JY, Yoon SJ, Kim JE, et al. Gray matter deficits in young adults with narcolepsy. *Acta Neurol Scand*. 2009; 119(1):61-7.
- [55] Jooy EY, Tae WS, Kim JH, Kim BT, Hong SB. Glucose hypo metabolism of hypothalamus and thalamus in narcolepsy. *Ann Neurol*. 2004; 56(3):437-40.
- [56] Brabec J, Rulsh A, Horinek D, Pala A, Guerreiro H, Buskova J, et al. Volume of the amygdala is reduced in patients with narcolepsy - a structural MRI study. *NeuroEndocrinolLett*. 2011; 32(5): 652-6.

#### PARTICULARS OF CONTRIBUTORS:

1. Intern, Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India
2. Associate Professor, Department of Obstetrics and Gynaecology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India.

#### NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Haritha Sagili,  
Associate Professor, Department of Obstetrics and Gynaecology,  
JIPMER, 12<sup>th</sup> Cross, Saradambal Nagar, Pondicherry-605005, India.  
Phone: 9489390630, E-mail: harithasagili@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Aug 08, 2013**  
Date of Peer Review: **Oct 09, 2013**  
Date of Acceptance: **Nov 28, 2013**  
Date of Online Ahead of Print: **Dec 27, 2013**  
Date of Publishing: **Feb 03, 2014**