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The Role of Autoimmunity in Narcolepsy
A Review

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Abstract

Narcolepsy is a lifelong hypersomnia with low prevalence worldwide. Narcoleptic patients have been highly associated with HLA-DQB1*06:02 which triggered an interest in the autoimmune possibility of this disorder's onset. Through the improvement of both technologies and techniques, further associations and hints of its mechanism were found, allowing for a continuous improvement on the knowledge of the disorder.

The discovery of orexins and orexinergic neurons was a major breakthrough that gave scientists the chance of focusing efforts on a specific cell. The later association with T cell receptors further suggested autoimmunity, but the lack of an autoantigen or inflammatory markers in narcoleptics suggested that that was not the case.

However, research continued and what could be later proven as another major breakthrough was just discovered, namely the C-amidated form of orexin. This molecule is secreted by orexinergic neurons and its half-life is short due to the C-terminal peptidase mediated degradation. It has been found to have high affinities toward DQ0602, showing that it could be the autoantigen scientists have been looking for.

Keywords

Sleep Disorders; Hypersomnia; Narcolepsy; Orexins; Autoimmunity

Resumo Alargado

A presente dissertação é uma tentativa de compilar informação acerca da narcolepsia num texto conciso e objetivo. Uma vez que a patofisiologia e a etiologia desta doença têm sofrido um grande desenvolvimento, serão estas áreas o foco principal do texto.

A narcolepsia é uma doença crónica rara com uma prevalência global de 25 a 50 indivíduos por 100 000. Faz parte do grupo de doenças do sono, mais particularmente, das hipersónias. Os doentes narcolépticos apresentam sonolência diurna excessiva, sono noturno perturbado, alucinações hipnagógicas e ataques de sono, com início na fase REM, com duração de poucos minutos. Alguns doentes apresentam também cataplexia, um sintoma patognomónico da narcolepsia que se traduz por perda bilateral do tónus muscular, repentina e temporária, em resposta a estímulos emocionais fortes, como riso, surpresa ou excitação sexual. A descoberta da associação entre a narcolepsia, a cataplexia e os níveis de orexina no líquor levou à divisão desta doença em dois tipos. O tipo 1 identifica os doentes com níveis de orexina A baixos e cataplexia, enquanto que o tipo 2 identifica os doentes narcolépticos sem estas características. O paradigma desta doença alterou radicalmente em 1983 (associação ao HLA-DR2), em 1998-1999 (descoberta das orexinas) e em 2009-2010 (associação à gripe A), e poderá sofrer uma nova revolução no futuro próximo devido à possível identificação do tão procurado auto-antigénio.

As orexinas, também chamadas de hipocretinas, são neurotransmissores excitatórios com funções associadas à promoção do estado de alerta, da ingestão alimentar e do consumo energético. Foram descobertas em 1998 por dois grupos de cientistas distintos, facto que explica a existência de dois nomes. As orexinas são secretadas por neurónios localizados no hipotálamo lateral. Estes neurónios produzem um péptido chamado de prepro-orexina, que sofre um processo de maturação, dando origem a dois neuropéptidos, a orexina A e a orexina B.

A ideia de que a narcolepsia poderia ser uma doença autoimune surgiu com a descoberta da sua forte associação ao haplótipo HLA-DR2 em 1983. Com o desenvolvimento de novas técnicas e tecnologias, a associação focou-se no alelo HLA-DQB1*06:02 e surgiram mais associações, como são exemplos os polimorfismos dos loci do TCRα, do OX40L e da catepsina H. De referir que todas estas moléculas estão associadas ao sistema imunitário.

Uma descoberta inesperada foi feita quando casos de narcolepsia surgiram depois de terem sido infetados pela gripe A de 2009 ou depois de terem sido vacinados para esta. A associação entre a narcolepsia e estes fatores foi suficiente para se considerarem como possíveis fatores causais, e fortalecer o papel da autoimunidade no desenvolvimento da doença.

No entanto, existem ainda algumas falhas a nível do conhecimento da patofisiologia da narcolepsia que impedem a classificação com certeza desta doença como autoimune. Uma destas falhas está na incapacidade de identificar um auto-antigénio. No entanto, estudos recentes indicam que um precursor da orexina, a orexina amidada, poderá ser o auto-antigénio que se tem procurado.

Mais investigação será necessária para comprovar ou negar esta hipótese.

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Abbreviations

APC	Antigen Presenting Cell
ATP	Adenosine Triphosphate
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CTSH	Cathepsin H
EEG	Electroencephalogram / -graphy
GABA	Gamma Aminobutyric Acid
HLA	Human Leukocyte Antigen
MCH	Melanin Concentrating Hormone
NREM	Non-Rapid Eye Movement Sleep
Orx	Orexin
OrxA	Orexin A
OrxB	Orexin B
Orx_{NH_2}	Amidated Orexin
OX1R	Orexin Receptor 1
OX2R	Orexin Receptor 2
REM	Rapid Eye Movement Sleep
TCR	T Cell Receptor

Chapter 1

Introduction

Narcolepsy was first described in the late 19th century.[1] In 1983, an association with the human leukocyte antigen haplotype HLA-DR2 was found, since the prevalence of this allele is very high in narcoleptics and much lower in other individuals. Research and technology further specified the allele HLA-DQB1*06:02 as the main association to narcolepsy. For a long time, that association was the only hint to the pathology of the disorder, until the discovery of orexins in 1998 and its later association with narcolepsy in 2000.[2] An autoimmune mechanism had been suspected, however it wasn't enough to label the disorder as autoimmune since it had no classical autoantibodies nor orexin or orexin receptor autoantibodies, no associated autoimmune diseases in the patient or the family, no CSF immunoglobulins synthesis or either T or B cell accumulation in the central nervous system and finally, no inflammation marker increase.[3] Therefore, in the beginning of the 21st century, narcolepsy was known as a hypersomnia with REM sleep disturbances and cataplexy, somehow caused by changes in the orexin pathway on genetically predisposed individuals. Since then, several technologies and techniques were developed, allowing for the association of further alleles and consequently, more cell types.

Furthermore, a recent peak of narcolepsy incidence in 2009/10, associated to the H1N1 influenza A pandemic allowed for a more focused research in a bigger pool of cases.[4,5] This resulted in better understanding of the underlying etiology and several mechanism proposals These mechanism proposals and further evidence showed that an autoimmunity mechanism is more than likely.

Taking into account how much knowledge of this disorder has evolved, it seems to be an appropriate moment to gather information and write a dissertation on the subject. Nevertheless, it must be taken into account that a lot of this information is less than a decade old, with a few months in some cases, and as such hasn't had time to be re-tested and confirmed or denied.

Objective

The present dissertation is an attempt at compiling data on narcolepsy into an objective and concise text. The focus is the disorder's pathophysiology and etiology, considering these were the areas that have seen more development. Both established facts and surfacing new data were analyzed. Ideally, this text would help fellow scientists and/or students with interest in the area to better understand narcolepsy, providing a starting point to its research and application of knowledge.

Methods

Taking into account how much narcolepsy as a pathology has evolved, in order to assemble this dissertation PubMed was used as a primary source of scientific articles starting July 2018. "Narcolepsy", "sleep disorder", "autoimmunity", "orexin", "hypocretin" and variations were the main keywords used in the search. The articles found were then selected according to several factors: Only articles in English were used; Newer articles were preferred over older ones; Articles with more citations were preferred, as were magazines with higher impact factors. Afterwards, articles were selected based on the information present in the abstract and the conclusion mainly. While studying the selected articles, some were removed since the information was deemed outdated or irrelevant to the subject.

The disorder paradigm changed a lot from 1998-1999 to 2009-10 to this day; therefore, newer information was considered more accurate.

Three books were also used to complement information on both sleep physiology and narcolepsy definition. These books were recommendations and the editions used were selected according to availability / access. All of these books have more recent editions; therefore, article information was considered more accurate and prevailed over book information on contradicting subjects.

Chapter 2

Sleep-Wake Cycle

The balance between states of consciousness, namely wake and sleep, is one that is still not fully understood. However, technologies and methods developed in recent years, including optogenetics[6-8] and pharmacogenetics[9-11], allow for a stream of new findings and further establishment of the physiology and regulation of sleep. Accordingly, it's not enough to regard sleep as a single identity.

A normal night's sleep can be divided into two different main states, rapid eye movement (REM) sleep and non-REM (NREM) sleep, forming cycles of about 90 minutes. Electroencephalography (EEG) is especially useful in the study of sleep and its stages. NREM sleep in humans amounts to about 80% of total sleep and is characterized by a synchronized pattern of large and slow EEG oscillations, and lack of cortical control. Furthermore, NREM sleep can be separated into four stages, from N1 to N4. N1 and N2 are considered light sleeps, N3 and N4 are deeper sleeps, with the latter being known as slow-wave sleep.[12] REM sleep was first described in the 1950s[13-15], and its name originates from the rapid eye movement that it presents. In NREM sleep EEG waves characteristically synchronize. On the other hand, EEG waves in REM sleep are desynchronized, making it more similar to wake than NREM sleep. However, this sleep state is paradoxically deeper, meaning that more stimuli or stronger ones are required to wake up. Also, the muscular tone is further decreased, but the cerebral cortex is very active. Concluding, NREM sleep is characterized by some nocturnal movements, but low brain activity, while REM sleep corresponds to a paralysis-like state[16], with increased brain activity and dreaming.

Sleep Regulation

Several brain regions have been associated with the sleep wake cycle. The reticular formation was one of the earliest.[17] Experiments have shown that lesions to these neurons result in drowsiness and its stimulation is responsible for the maintenance of the alert state by direct and indirect stimulation of the cortex. Involved in this process are cholinergic (laterodorsal tegmental nucleus and pedunculopontine tegmentum nucleus)[18], noradrenergic (locus coeruleus)[19], serotonergic (raphe nuclei)[20], and dopaminergic (ventral tegmental area, substantia nigra and periaqueductal gray)[21] neurons.

Another wake promoting region is the posterolateral hypothalamus. This region is responsible for orexin (Orx, also known as hypocretin) production, a neuropeptide involved in sleep wake regulation, feeding, thermoregulation, blood pressure and neuroendocrine regulation.[22]

Disturbances of this neurotransmitter's function are the most likely culprits behind narcolepsy.[23] Furthermore, the tuberomammillary nuclei have wake promoting functions through histaminergic neurons.[24,25] This may explain why antihistamines have a soporific effect.

Likewise, other regions have proven important to induce and maintain sleep. The anterior hypothalamus, specifically the preoptic area is related to sleep onset.[26] Besides promoting sleep, inhibition of wake active cells is needed to sleep. This role is carried out by neurons located in the ventrolateral preoptic area, median preoptic area and medullary parafacial zone.[27] Substances such as prostaglandin D2 and adenosine activate these neurons (particularly interesting since adenosine results from the breakdown of the body's main source of energy, ATP), triggering a mechanism based on the actions of gamma aminobutyric acid (GABA) and melanin concentrating hormone (MCH). MCH is a neuropeptide with inhibitory functions, acting through the G-Protein coupled receptor MCHR1. MCH and Orx were found to be mutually inhibitory and coextensive, though not colocalized, which lead to the belief that these neurotransmitters and their interaction may be key to sleep regulation.[28]

This mechanism would be simple enough, however, as was stated before, it's not enough to regard sleep as a single identity. Therefore, REM and NREM promoting cells must be distinguished. Neurons with firing rates decreasing from wake to REM are called REM-off cells (aminergic), and by the same logic, neurons most active in REM sleep are called REM-on cells (cholinergic).[29] REM-off and REM-on cells are found together in a variety of brain regions which suggests an interaction between them. The REM-on cells on the dorsolateral pons are especially important in the induction of REM sleep and its characteristics, meaning EEG waves, rapid eye movement and atony. Projections from the dorsolateral pons to inhibitory neurons in the ventral medulla, result in spinal motor neurons inhibition and cause the paralysis-like state typically associated with REM. Disorders in this mechanism result in a condition known as REM behavior disorder in which the patient moves as if acting out dreams.[30]

Regulation of sleep is an intricate physiological mechanism that is currently explained by a two-process model, named Process C (for circadian cycle) and Process S (for sleep pressure). Process C is the more fully understood part of this model.[31] It is associated to a biological clock / circadian pacemaker, located in the hypothalamic suprachiasmatic nucleus. Neurons in this nucleus present a particular pattern of firing resembling the 24-hour cycle. Some physiological mechanisms help regulate process C even without suprachiasmatic nucleus' intervention, forming a peripheral clock. Process S has historically been more elusive. Since it represents the homeostatic sleep pressure, process S directly relates to the amount of time awake and is thought to be directly dependent on the balance between MCH and Orx.[32]

Orexins

Orexins are excitatory neuropeptides that promote wake, food intake and energy expenditure.[33] Orexinergic neurons are located exclusively in the lateral hypothalamus and project to several areas inducing a myriad of effects. Through the activation of the locus coeruleus (noradrenergic), tuberomammillary nucleus (histaminergic) and raphe nucleus (serotoninergic), orexins are able to promote wakefulness. On the other hand, GABAergic neurons on the ventrolateral preoptic area inhibit orexinergic neurons, promoting sleep.[34] Furthermore, orexins impact the reward system through dopaminergic neurons in the ventral tegmental area, and receive input from the limbic system.[35] Regarding the food intake and energy balance, orexinergic neurons are inhibited by anorexigenic stimuli such as glucose and leptin increase and stimulated by the orexigenic peptide ghrelin.[36] Also relevant to the energy expenditure control is the sympathetic tone facilitated by orexins.[37]

The process of Orx production begins with the production of a peptide named prepro-orexin. This peptide will go through a maturation process, resulting in the formation of two excitatory neuropeptides, orexin A (OrxA) and orexin B (OrxB). For the purpose of this text, Orx will be used to represent orexins as a group. These neurotransmitters act by way of two receptors, OX1R and OX2R, expressed throughout the central nervous system (CNS). OX1R is a Gq-protein coupled receptor, selective for OrxA, with dominant expression in the arcuate nucleus, ventrolateral and lateral hypothalamus and tuberomammillary nucleus.[38] OX2R is coupled to both Gq and Gi/o, non-selective and dominantly expressed in the locus coeruleus. Both receptors are expressed in the raphe nucleus and ventral tegmental area. The increased sleepiness seems to be related to OrxB while both OX1R and OX2R pathways seem to be implicated in the REM sleep dysregulation.[39]

In 1998, two groups of scientists discovered these neuropeptides and their relationship to feeding. Sakurai et al.[38] named these neuropeptides orexins while de Lecea et al.[40] named them hypocretins, this being the reason why both names are accepted. In 2000, Nishino et al.[23] presented the first reports of orexin deficiency in narcoleptics with cataplexy. In that same year, Peyron et al.[41] found that only one out of seventy-four narcoleptic patients had an orexin system mutation with a consequent early onset. Postmortem examination by Thannickal et al.[42] in following studies revealed orexinergic neurons reduced by 85-95% with no relevant damage to MCH neurons, indicating selectivity of neuron destruction and further suggesting an autoimmune process.

Chapter 3

Narcolepsy

Narcolepsy is a rare chronic sleep disorder in the hypersomnia specter with a global prevalence of 25 to 50 per 100 000 people.[43] Narcoleptic individuals have excessive daytime sleepiness, disturbed nocturnal sleep, hypnagogic hallucinations and brief episodes of sleep attacks with REM onset typically lasting a few minutes occur frequently during the day, interrupting wake. The onset of sleep can be abrupt, with potentially disastrous consequences. Some patients also present cataplexy, a pathological response to strong emotional stimuli such as laughter, surprise or sexual arousal, which entails a temporary sudden bilateral loss of muscle tone without loss of consciousness, much like the REM sleep physiological muscle paralysis. Cataplexy is a pathognomonic symptom of narcolepsy.[44] Analytically, most narcoleptics have an OrxA deficiency in the cerebrospinal fluid (CSF), and these are the ones who present cataplexy. Earlier on the classification of the disease, it was coded as narcolepsy with cataplexy or without. However, the association between cataplexy and Orx levels lead to the inevitable reclassification of the disorder as type 1 or type 2, with type 1 corresponding to narcolepsy with cataplexy and/or OrxA CSF levels of under 110 pg/mL. Narcolepsy type 2 diagnosis requires the same multiple sleep latency test results as has been used for narcolepsy diagnosis (<8 minutes) associated with two sleep-onset REM periods, without cataplexy or low OrxA CSF levels.[45]

Clinically, narcoleptics are treated symptomatically. Excessive daytime sleepiness is treated with stimulants such as methylphenidate and modafinil to increase their overall level of arousal and a strong sedative for overnight sleep, sodium oxybate. Recommended drugs for cataplexy are sodium oxybate, venlafaxine, other serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors and atomoxetine. Tricyclic antidepressants such as venlafaxine and protyptiline are used for cataplexy, but anticholinergic adverse effects are limiting. Reboxetine and mazindol have also been used.[46] Plasmapheresis[47], alemtuzumab[48] and intranasal OrxA[49] have been attempted with limited success. Steroids have shown no beneficial effect.[50] Overall, narcolepsy symptoms reduce over time even without symptomatic treatment. Adding the fact that drugs targeting immune or CNS cells have serious side effects, it begs the question of whether narcoleptics should be medicated beyond major symptoms.[51]

Animal experiments in dogs and mice indicate that mutations in the OX2R locus can cause both hyperexcitability of the neurons that generate REM sleep and impairment of the circuitry responsible for REM sleep inhibition.[52] Furthermore, Orx-producing neurons are selectively destroyed in narcoleptic patients. The destruction of these neurons seems to be gradual with an onset age between 10 and 30 and follows a seasonal pattern of onset, with increased

incidence in spring and summer. This is explained by winter infections (*Streptococcus pyogenes* and influenza A) onset with a five-month delay before development of symptoms related to loss of Orx-neurons (>80%).[53] Further supporting the seasonal onset is the association that has surfaced between specific viral and bacterial infections and narcolepsy onset. One such example dates back to the end of the first world war, namely the Spanish flu. Some patients presented a variation of the disease that was known as encephalitis lethargica. These patients entered a state of coma, which often resulted in death. Autopsies revealed lesions to the posterior hypothalamus, the same region that is associated to hypersomnia and where orexin-producing neurons are located.[17] More recently, Streptococcus pyogenes infection with seric antibodies[54] and the 2009 H1N1 influenza A pandemic case brought narcolepsy to the spotlight. Evidence shows that both infected individuals and certain vaccinated individuals developed narcolepsy. In question is the AS03-adjuvanted pH1N1 vaccine named Pandemrix, used mostly in Northern Europe countries; other vaccines were used with no relevant increase in narcolepsy incidence.[55,56]

It seems that there is a compensation mechanism to the loss of wake promoting Orx by increasing the number of histaminergic neurons.[57] The implications of this discovery are yet to be tested. However, new medications aiming to improve histamine signaling are being developed and tested with the goal of reducing overall sleepiness and the frequency of cataplexy episodes. One such drug, pitolisant, has been the focus of recent studies and has been shown to have similar effects compared to modafinil, with better tolerance.[58]

Autoimmunity

The etiology of narcolepsy seems to lead to orexins, orexin receptors and orexin-producing neurons. However, even before orexins were discovered, genetic evidence suggested an autoimmune mediated mechanism as the basis of the disorder. Narcolepsy has been associated with human leukocyte antigen HLA-DR2 haplotype since 1983[2] and it currently has one of the highest HLA subtype associations known. Several autoimmune diseases had been associated with HLA class II loci, including rheumatoid arthritis, type 1 diabetes and Graves' disease, establishing both a chance of the disorder being autoimmune based and a requirement for further research. Continuing investigation and technological improvements pinpointed to the HLA-DQB1*06:02 allele, in the HLA class II locus, since over 85% of narcoleptics with cataplexy have it, often combined with HLA DRB1*15:01, against 12-38% of the general population. About 50% of patients with atypical, mild or narcolepsy without cataplexy have HLA-DQB1*06:02.[59]

Another piece of the immune system has gained relevance in narcolepsy research, ever since T cell receptor α loci polymorphisms were found, through the use of genome wide association, to be highly prevalent in narcoleptics. Most T cells have a T cell receptor (TCR) consisting of two glycoproteins named TCRα and TCRß.[60] TCRs are surface receptors responsible for antigen recognition and its follow-up. Simplifying, TCRs of CD8+ cells will recognize antigens presented by HLA class I molecules and TCRs of CD4+ cells will recognize antigens presented by HLA class II molecules. An example of these HLA class II molecules is DQ0602, a heterodimer consisting of α and ß monomers, encoded by the DQB1*06:02 and, in most cases, DQA1*01:02 or DRB1*15:01 alleles.[61] Adding to this are mice experiments showing that CD4+ T cells migrate to the proximity of orexin neurons, inducing neuron death via CD8+ cell action.[62] This is yet to be shown on humans.

Furthermore, weaker associations were made between narcolepsy and loci for tumor necrosis factor family member 4 (TNFSF4) also known as OX40 antigen ligand (OX40L), important for antigen processing and T cell stimulation; cathepsin H (CTSH); and purinergic receptor subtype P2Y11 to DNA methyltransferase 1, P2RY11-DNMT1, highly expressed in CD8+ T cells and associated with a clinical phenotype comprising narcolepsy with cataplexy, deafness, cerebellar ataxia and dementia.[63] Also of note are the facts that DNMT1 is important for neural survival and neurodegeneration; and that hypomethylation has been associated to lupus among other autoimmune diseases.

All of this evidence points towards autoimmunity, however classical autoimmune disease signs are not found in narcolepsy. Autoantibodies to orexin or orexin receptor were not consistently positive, there were no associated autoimmune diseases in the patient or the family, no CSF immunoglobulins synthesis or either T or B cell accumulation in the central nervous system and finally, no inflammation marker increase.[3]

The protein TRIB2 was suspected to be related to narcolepsy in the years surrounding the 2009 pandemic, since it was found to have much higher antibody titers in narcoleptic patients than in controls.[64] However, these results were not reproduced in later studies[65], which ruptured the connection to narcolepsy.

Among several hypotheses that have been suggested, cellular/molecular mimicry has been the most likely.[53] The molecular mimicry hypothesis suggests that the interaction between DQ0602 and either H1N1 influenza epitopes or Pandemrix vaccine that activates CD4+ T cells can be mimicked by an autoantigen with similar structure or sequence, inducing its detection by TCR as foreign and the consequent autoimmune response.

A more complete mechanism to this hypothesis, including molecules associated with narcolepsy goes as follows: Antigen presenting cells (APC) will phagocyte H1N1 influenza virus and break it down in the lysosome with the help of several enzymes, including CTSH. From this hydrolysis, resulting peptides will be presented on the surface of the APC in an HLA class II (DQ0602) to the TCR of CD4+ T cells. These CD4+ cells will then upregulate OX40, a costimulatory receptor which is activated by the OX40L present on APCs, further stimulating cell activation. The activated CD4+ cell will then release cytokines stimulating a CD8+ T cell immune response. The migration of these immune cells to the CNS facilitates the interaction with CNS APCs (microglia) which would present orexinergic neuron specific autoantigens through DQ0602 (identified as foreign through molecular mimicry), inducing CD8+ T cell effector function resulting in cell death.[66] However, for this hypothesis to be viable, there must be some kind of autoantigen specific to Orx or orexinergic neurons that is in fact detected by TCRs. No such autoantigen has been reported until just a few months ago.

Autoantigen Proposal

Luo et al.[53] have confirmed that Orx itself cannot be this autoantigen. However, they have found the autoantigen to be a premature version of it. As has been explained earlier in this text, Orx results from the maturation of prepro-orexin. However, this maturation process involves the C-terminal amidation of Orx, a posttranslational modification required for biological activity. These amidated orexins (Orx_{NH_2}) are secreted by orexinergic neurons, being degraded by C-terminal peptidases rapidly. The Orx_{NH_2} have been shown to have higher affinities for DQ0602 in comparison to Orx. Adding to that is the fact that the half-life of Orx_{NH_2} is very short, justifying its low presence outside the immediacies of orexinergic neurons. The lack of contact with the thymus may allow it to bypass central tolerance establishment, increasing the risk of autoimmunity.

Chapter 4

Conclusion

Narcolepsy is a multifactorial disease and its development depends on both genetic predisposition and environmental triggers. The genetics of narcolepsy have been associated to autoimmunity for a long time, however, new genetic associations are found every year, but none has shown such a high connection as HLA-DQB1*06:02. Environmental triggers have been found in influenza A H1N1 virus, its AS03 adjuvanted vaccine Pandemrix and Streptococcal infections.

The association with orexins made narcolepsy research much more rewarding as the cells in study are much more focused and positive results are more often achieved. This association led to the thorough search for autoantigens in orexinergic neurons. Apparently, this autoantigen was finally revealed, but like everything new in science, more research and evidence are needed to confirm this is the case.

If amidated orexin is proven an undoubtful autoantigen towards the onset of narcolepsy, the mechanism steps will surely follow. From this, prevention and better treatment for narcoleptics can arise, allowing for a better quality of life in this population.

Concluding, the role of cellular immunity in the onset of narcolepsy is still in question since the literature available today is not enough to guarantee autoimmunity as the undoubtful cause of narcolepsy. However, strong genetic evidence and strong associations to infections and vaccination are predictive of this being the case. Further research is needed to establish a definitive mechanism allowing for the best possible treatment of narcoleptic patients.

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