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Narcolepsy, cataplexy, hypocretin and co-existing other health complaints: A review

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Abstract: The presence of cataplexy in people with narcolepsy has a well-documented tight association with very low or non-detectable levels of the central nervous system neuropeptide, hypocretin (also termed orexin) while levels of hypocretin are normal in people with narcolepsy without cataplexy. There is evidence to suggest that hypocretin may have an association with pain, migraines and headaches in people with narcolepsy. However, these studies have not compared findings across narcolepsy with and without cataplexy. Currently, there are no studies published to determine whether pain, migraines and headaches are just common symptoms experienced by all people with narcolepsy or whether the presence of the cataplexy symptom (and thus assumed low levels of hypocretin) exacerbates these symptoms. Also, it is unclear whether general health and wellbeing (including psychological wellbeing) is similarly affected by hypocretin levels, or may be confounded by different levels of other health symptoms, such as pain. This review poses a number of research questions that need to be explored about whether the presence or absence of cataplexy is differentially associated with different types, severity and location of chronic pain; frequency, location and types of migraines and headaches; and general health and wellbeing among people with narcolepsy. A greater understanding of the role of hypocretin in these health complaints could aid in the development of more appropriate treatments for pain, migraines and headaches amongst people with and without narcolepsy.

Subjects: Psychological Science; Behavioral Neuroscience; Health and Social Care

Keywords: narcolepsy; cataplexy; pain; migraines; headaches; hypocretin

ABOUT THE AUTHORS

Our research group focuses on examining a range of health issues amongst people with narcolepsy with and without cataplexy. The presence of cataplexy in people with narcolepsy has a well-documented tight association with very low or non-detectable levels of the central nervous system neuropeptide, hypocretin (also termed orexin) while levels of hypocretin are normal in people with narcolepsy without cataplexy. There is evidence to suggest that hypocretin may have an association with pain, migraines and headaches in people with narcolepsy. However, these studies have not compared findings across narcolepsy with and without cataplexy. Our research group aims to provide supportive data to move a step closer to addressing the current gaps in the literature.

PUBLIC INTEREST STATEMENT

This review paper discusses current research examining the differences between narcolepsy with and without cataplexy (and thus presumed different hypocretin levels), with a focus on pain, migraines/headaches and general health and wellbeing in narcolepsy. Specific research questions that need to be answered are posed. Answers to these questions are important as they will lead to a greater understanding of the role of hypocretin, the aetiology of selected health issues in people with narcolepsy and potentially aid in the development of more appropriate treatments for pain, migraines and headaches.

1. Introduction

Narcolepsy is a disabling sleep disorder with an estimated mean prevalence of approximately 30 per 100,000 people (Abde-Khalek, 2001; Cave, 1931; Daniels, 1934; Martikainen, Hasan, Urponen, Vuori, & Partinen, 1992; Ozdemir et al., 2005; Partinen & Hublin, 2005; Schmitt, Gugger, Augustiny, Bassetti, & Radanov, 2000; Schwegler et al., 2006; Szklo-Coxe, Young, & Mignot, 2003; The Gallup Organization, 1997; Young et al., 1993). American studies have estimated a higher prevalence of 56 per 100,000 (Silber, Krahn, Olson, & Pankratz, 2002). However, other studies have estimated a much lower prevalence rate of 15 per 100,000 people (Shin et al., 2008). These prevalence rates reflect both narcolepsy with and without cataplexy. Some researchers have attempted to identify the prevalence rate of narcolepsy with and without cataplexy separately. It is now estimated that the prevalence for narcolepsy with cataplexy is between 25 to 50 per 100,000 (Longstreth, Koepsell, Ton, Hendrickson, & van Belle, 2007; Nohynek et al., 2012; Partinen et al., 2012) and 20 to 34 per 100,000 for narcolepsy without cataplexy (Shin et al., 2008; Silber et al., 2002). Narcolepsy can develop at any age; however, research has identified bimodal peak ages of onset of 14.7 and 35 years, with an average age of 16 (Silber, Krahn, & Slocumb, 2005). Often, if age of onset is in the teenage years there is a higher frequency of cataplexy experienced by the diagnosed individual (Krishnamurthy, Nallamothu, & Singareddy, 2014). A family history of narcolepsy is uncommon; however, family members are at an increased risk of 1–2% for first degree relatives (Billiard et al., 1994; Mathew, 1994). Twin studies have also found a low concordance rate between monozygotic twins, with a 25% concordant for type 1 narcolepsy and 32% when looking at both type 1 and type 2 narcolepsy (Mignot, 1998). This sleep disorder has a negative effect on quality of life regardless of diagnostic or medication status (Daniels, King, Smith, & Shneerson, 2008; Ervik, Abdelnoor, Heier, Ramberg, & Strand, 2006; Goswami, 2012; Kim et al., 2015; Rovere, Rossini, & Reimão, 2008). Quality of life is reduced due to the associated symptoms experienced with narcolepsy, the impairment it imposes on everyday living and the psychological symptoms that are expressed by an individual (Daniels et al., 2008; Kim et al., 2015). For a diagnosis of narcolepsy to be made, severe daytime sleepiness must be present. Also, one or more of the following symptoms *may* be present: sleep-onset or sleep-offset paralysis and/or hallucinations and frequent movement and awakenings during sleep. A Multiple Sleep Latency Test (MSLT) is used to help make a diagnosis. The MSLT is a sleep disorder diagnostic tool that can distinguish between normal from abnormal daytime sleepiness (Dement, Mitler, Roth, Westbrook, & Keenan, 1986). A key feature of the MSLT and narcolepsy is a mean sleep latency of less than 8 min and two or more sleep-onset REM periods (Dement et al., 1986). To be diagnosed with narcolepsy *with cataplexy*, severe daytime sleepiness must be present and accompanied by episodes of a sudden loss of muscle tone, which are triggered by emotional arousal (Dauvilliers, Arnulf, & Mignot, 2007). The sudden loss of muscle tone can be partial (e.g. affecting the face and/or neck) or complete, resulting in a full body collapse. When a cataplexy attack occurs it usually lasts between 1 and 2 min and the individual remains conscious. Approximately two thirds of people with narcolepsy suffer from cataplexy (Thannickal, Nienhuis, & Siegel, 2009). With the publication of the International Classification of Sleep Disorders – second edition in 2005, a formal distinction between narcolepsy with and without cataplexy was made. In 2014, The American Academy of Sleep Medicine (2014) determined that narcolepsy would be diagnosed as either narcolepsy type 1 (narcolepsy with cataplexy) or narcolepsy type 2 (narcolepsy without cataplexy); therefore, for the remainder of this paper, narcolepsy with cataplexy will be referred to as narcolepsy type 1 and narcolepsy without cataplexy as narcolepsy type 2.

This review paper will present a brief history of cataplexy, its purported link to the neuropeptide hypocretin, and discuss key theories about how hypocretin may be involved in the symptoms of cataplexy and sleepiness. It will then discuss current research examining the differences between type 1 and type 2 narcolepsy (and thus presumed different hypocretin levels), with a focus on pain, migraines/headaches and general health and wellbeing in narcolepsy. Specific research questions that need to be answered will be posed. Answers to these questions are important as they will lead to a greater understanding of the role of hypocretin, the aetiology of selected health issues in people with narcolepsy and potentially aid in the development of more appropriate treatments for pain, migraines and headaches.

2. The discovery of hypocretin's role in narcolepsy

People with type 1 narcolepsy have been found mostly to have low or non-detectable levels of hypocretin, whereas people with type 2 narcolepsy typically have normal levels (Dauvilliers et al., 2003; Heier et al., 2007; Kanbayashi et al., 2002; Krahn, Pankratz, Oliver, Boeve, & Silber, 2002; Savvidou et al., 2013). However, other studies have found that 10–30% of people with type 2 narcolepsy have low levels of hypocretin (Andlauer et al., 2012; Baumann et al., 2014). The neuropeptide hypocretin, which is also referred to as orexin, is involved in sleep and wakefulness. This neuropeptide is produced in the lateral hypothalamus of the brain (Davis, Choi, & Benoit, 2011). Abnormally low hypocretin levels may be associated with other neurological conditions such as epilepsy (Rejdak, Papuć, Grieb, & Stelmasiak, 2009), Hashimoto's encephalopathy (Castillo, Mignot, Woodruff, & Boeve, 2004) and head trauma (Ripley et al., 2001) (see Table 1). However, there is no evidence to suggest the symptom of cataplexy exists among these neurological disorders.

The discovery of hypocretin was made in 1998 by two independent research groups, and this led to the neuropeptide having two names. One group (Sakurai et al., 1998) named it orexin, meaning "appetite" in Greek due to its involvement in food intake, and the other group (de Lecea et al., 1998) named it hypocretin due to the location in the brain where it is produced. For the purpose of this review paper, the neuropeptide will be referred to as hypocretin. Two years after hypocretin itself was identified, the link between low hypocretin in cerebrospinal fluid, loss of hypocretin cells and narcolepsy was observed (Crocker et al., 2005; Mignot et al., 2002; Peyron et al., 2000; Thannickal et al., 2000; Valko et al., 2013), and led to the proposal that narcolepsy is caused by a loss of hypocretin cells when compared to healthy brains. It is unclear as to why there is a loss of hypocretin cells and wether people with a loss of hypocretin cells were born this way or if the loss occurred over time (Blouin et al., 2005; Nishino, Ripley, Overeem, Lammers, & Mignot, 2000; Peyron et al., 2000; Thannickal et al., 2000). However, it is understood that this loss leads to a reduction in the levels of hypocretin that is produced (Blouin et al., 2005; Nishino et al., 2000; Peyron et al., 2000; Thannickal et al., 2000). The loss of hypocretin cells refers to the cells that are located in the hypothalamus, which produce the neuropeptide hypocretin. A study that examined deceased brains of people with narcolepsy and people without any neurological disorders found that people with narcolepsy had 85–95% less hypocretin cells compared to the brains without any neurological disorders (Thannickal et al., 2000). However, it was later revealed that lower hypocretin levels were mostly linked to cataplexy, which does not occur in approximately one-third of all people with narcolepsy (Thannickal et al., 2009). When brains of deceased people with type 2 narcolepsy were examined, it was found that there was only a 33% reduction in hypocretin cells compared to brains of deceased people without narcolepsy or any neurological disorders (Thannickal et al., 2009). Nevertheless, people with type 2 narcolepsy have been found to have a normal level of hypocretin in their cerebrospinal fluid (Mignot et al., 2002). Thannickal et al. (2009) theorised that people with narcolepsy either do or do not experience cataplexy depending on whether there has been a significant loss of hypocretin cells. That is, if an individual has lost a high percentage of hypocretin cells, this will cause them to experience cataplexy. However, the role of hypocretin in type 2 narcolepsy is not clearly understood.

3. Theories regarding hypocretin and narcolepsy symptoms

Some theories have been developed as to why low to non-detectable levels of hypocretin may be associated with cataplexy and sleepiness in people with narcolepsy. However, the actual physiological mechanisms underpinning these two key aspects of narcolepsy, and a well-developed theoretical understanding, supported by evidence, of how hypocretin loss may increase sleepiness and/or lead to cataplexy has not yet been achieved.

3.1. Hypocretin and sleep state instability

Sleep state instability (also known as 'behavioural state instability') is a condition whereby the period of being awake is short and REM and non-REM sleep become mixed up with each other (Mochizuki, Crocker, McCoemack, Yanagisawa, & Sakurai, 2004). This condition causes fragmented sleep and wakefulness. This low threshold becomes apparent when observing and monitoring "orexin knockout" mice during sleep and wakefulness. These mice have been genetically modified not to produce

Table 1. Sleep and neurological disorders—association with hypocretin, pain and migraines

	Hypocretin level	Experience cataplexy	Experience pain	Experience migraines/ headaches	Reference
Sleep disorders					
Narcolepsy with cataplexy	Low hypocretin levels and loss of cells	Yes	Yes	Yes	Castillo et al. (2004), Dauvilliers et al. (2007, 2011), Mignot et al. (2002)
Narcolepsy without cataplexy	Loss of hypocretin cells	No	Further research is required	Further research is required	Weder-Cisneros et al. (2004)
Idiopathic hypersomnia	Normal hypocretin levels and cell status unknown	No	Further research is required	Further research is required	Mignot et al. (2002)
Kleine Levin syndrome	Low hypocretin levels during an episode	No	No	Further research is required	Li et al. (2013); Dahmen et al. (2003)
Neurodegenerative diseases					
Alzheimer's disease	Low hypocretin levels and cell loss	No	No	Yes	Ebrahim et al. (2003), Thannickal et al. (2009)
Dementia	Reduced neocortical hypocretin-immunoreactivity	No	Yes	Further research is required	Donnelly and Leschziner (2016), Taiwo et al. (2007)
Parkinson's disease	Low hypocretin levels and cell loss	Yes	Yes	No evidence	Fronczek et al. (2008), Ylikoski, Martikainen, Sarkanen, and Partinen (2015)
Huntington's disease	Loss of hypocretin cells	No	No	No evidence	Wolfe, Ross, Anderson, Russell, and Hebert (1995)
Motor neurone disease	No research available	No	Yes	No evidence	McDermott and Shaw (2008)
Demyelinating diseases of the central nervous system					
Guillain-Barre syndrome	Low hypocretin level	No	Yes	No evidence	Fronczek et al. (2008)
Multiple sclerosis	HLA DR15 positive	Yes	Yes	No evidence	Binder et al. (2016), Sandyk (1995)
Peripheral neuropathies	No evidence	No	Yes	No evidence	Schestatsky (2007)
Autoimmune diseases					
Inflammatory bowel disease	HLA DR2 positive	No	Yes	Yes	Orrell (2010), Peterson, Frank, Pace, and Gordon (2008), Rejdak et al. (2009)
Rheumatoid arthritis	HLA DR2 positive	No	Yes	Yes	Farmakidis, Inan, Milstein, and Herskovitz (2015), Nishino (2003), Syvertsen et al. (2007)
Hashimoto disease	Low hypocretin level	No	Yes	No evidence	Farmakidis et al. (2015), Rainero et al. (2011)
Miscellaneous neurological conditions					
Acoustic schwannoma	Low hypocretin level	No	No	Yes	Ehde, Osborne, Hanley, and Kraft (2006), Schmidt, Williamson, and Ashley-Koch (2007)
Fibromyalgia	Normal	No	Yes	Yes	Myung and Jin-Sang (2004), Nampiaparampil (2008)
Epilepsy	Low hypocretin level	No	No evidence	Yes	Baumann et al. (2007), Mainieri et al. (2015)
Migraines	Genetic association with HCRTR1 gene	No	No evidence	Yes	Theeler and Erickson (2009)
Head trauma	Loss of hypocretin neurons	Yes	Yes	Yes	Bruck and Broughton (2004), Choy (2012), Dimitrova et al. (2011), Strohmaier, Mueller-Eckhardt, and Meier-Ewert (1988)
Encephalitis	Low hypocretin levels	Yes	No	Yes	Overeem, Reijntjes, Huyser, Jan Lammers, and Gert van Dijk (2004), Silva (2013)
Drop attacks	Status unknown	Yes	No	No	Egel, Lee, Bump, and Javois (2012)

hypocretin. When the orexin knockout mice were compared to mice that had not been genetically modified, the orexin knockout mice had much briefer periods of wakefulness and REM sleep and they transitioned between states much more often (Mochizuki et al., 2004). The same pattern was found among dogs with genetic mutations in genes that encode for hypocretin receptors (Nishino et al., 2000). That is, during periods of wakefulness hypocretin would activate neurons in particular sections of the brain that are associated with being awake to help maintain a wakeful state, and in turn neurons are activated to help maintain a state of sleep. This theory suggests that hypocretin is what creates a boundary between states of sleep and wakefulness. As mentioned, people with type 2 narcolepsy have been found to have normal levels of hypocretin (Thannickal et al., 2009). Therefore, for this theory to account for people with type 2 narcolepsy, there would have to be a deficiency with the amount of neurons that produce hypocretin and not the amount of hypocretin found in the cerebral spinal fluid (Thannickal et al., 2009).

3.2. Theories regarding cataplexy

It has been theorised that a cataplexy attack is actually REM sleep occurring during wakefulness (Burgess & Scammell, 2012). Cataplexy mimics the physiological response of REM sleep in that during REM sleep all skeletal muscles become paralysed. The only muscles that do not become paralysed are those around the eyes or involved in eye movements and the respiratory system. This is known as sleep atonia. This is what appears to occur during a cataplexy attack (Burgess & Scammell, 2012). Research has found that during REM sleep the release of norepinephrine and serotonin is suppressed (Winokur & Demartinis, 2012). Norepinephrine and serotonin are neurochemicals involved in the sleep-wake process. During wakefulness these neurochemicals are released to block REM sleep from occurring. It is hypothesised that when there are low or non-detectable levels of hypocretin the release of norepinephrine and serotonin is reduced. With a reduction in norepinephrine and serotonin a cataplexy attack occurs which resembles REM sleep during wakefulness (Burgess & Scammell, 2012).

However, this theory has been criticized. It is well documented that emotions trigger a cataplexy attack (Krahn, Lymp, Moore, Slocumb, & Silber, 2005; Sturzenegger & Bassetti, 2004) but this theory does not account for emotions triggering cataplexy (Overeem, Lammers, & van Dijk, 2002). Moreover, emotions do not trigger REM sleep and therefore do not trigger sleep atonia (Overeem et al., 2002). Instead, the theory of tonic immobility is proposed (Overeem et al., 2002). Tonic immobility can be described as, when an animal is faced with danger, they experience severe motor inhibition but remain fully conscious (Ginsburg, 1975). It is believed that strong emotions, such as fear, can trigger this response (Ginsburg, 1975). This theory could explain cataplexy in humans (Overeem et al., 2002), extending the explanation to other strong emotions beyond fear.

Not much is known as to why strong positive emotions, such as laughter, will often trigger a cataplexy attack. It has been theorised that the amygdala and prefrontal cortex play a role, as these particular areas of the brain become active both when an individual expresses positive emotions (Burgess, Oishi, Mochizuki, Peever, & Scammell, 2013; Oishi et al., 2013) and during cataplexy (Oishi et al., 2013). The rationale behind this theory is that when positive emotions activate the amygdala and prefrontal cortex in people with type 1 narcolepsy, abnormal activity occurs in these areas of the brain, triggering a cataplexy attack (Oishi et al., 2013). When individuals with type 1 narcolepsy are shown humorous pictures, areas of the brain that are involved with the hypocretin system are activated. It is believed that this system may be impaired in people with type 1 narcolepsy due to a hypocretin deficiency. This impairment causes humour to trigger a cataplexy attack (Schwartz et al., 2008). Interestingly, negative and neutral emotions, such as anger and surprise, also trigger a cataplexy attack (Sturzenegger & Bassetti, 2004).

Given that research has found that the left side of the prefrontal cortex is activated when negative emotions, such as anger and aggression, are expressed (Harmon-Jones & Sigelman, 2001), this theory can also account for negative emotions. How the role of the amygdala and prefrontal cortex in cataplexy may interact with the loss of hypocretin producing cells in the lateral hypothalamus has not yet been addressed in these theories (Oishi et al., 2013).

Another theory is that narcolepsy is caused by an autoimmune disease (Partinen et al., 2014). This theory proposes that the immune system attacks the neurons that produce hypocretin. This was seen with the 2009 influenza A H1N1 pandemic and vaccination with Pandemrix (Jacob et al., 2015; Saariaho et al., 2015). There was an increase in the diagnosis of narcolepsy with individuals who received one of these vaccinations. It was believed that this vaccination triggered an immune response in some individuals that were already susceptible to narcolepsy. A particular antibody called Anti-GM3 was identified as being associated with the HLA-DQB1*0602 narcolepsy gene. These antibodies were seen more frequently in individuals who received one of the vaccinations then individuals who did not (Saariaho et al., 2015).

4. Current and further hypocretin research

The role of hypocretin is currently being studied more closely across a range of behaviours and it is now known also to play an important role in appetite and humour. Research has found that appetite and arousal are activated by hypocretin (Preti, 2002; Tsujino & Sakurai, 2013). It has been known for several decades that damage to the lateral hypothalamus produced aphagia and weight loss whereas damage to the ventromedial nucleus of the hypothalamus resulted in hyperphagia and obesity (Bernardis & Bellinger, 1996; Oomura, 1980). Hypocretin, produced in the lateral hypothalamus, was subsequently found to activate appetite regulation and triggers food seeking and feeding behaviour (Sakurai, 2006). Also, research has found that the hypocretin system modulates human emotions; in particular, humour (Schwartz et al., 2008).

A number of findings (discussed below) suggest links between hypocretin activity and pain, headaches and migraines in people without narcolepsy. Furthermore, research has found that chronic pain (Dauvilliers et al., 2011), migraines (Dahmen et al., 2003), headaches (Miyamoto, Suzuki, Miyamoto, & Hirata, 2014) and reduced health and wellbeing (Dauvilliers et al., 2011) are significantly more common in people with narcolepsy than people without a disorder of daytime sleepiness. Reduced health and wellbeing refers to psychological symptoms such as depression, stress and anxiety experienced by an individual. It is unclear whether these symptoms are simply common among people with narcolepsy due to their sleep/wake problems or whether there is a specific link between these symptoms and low to non-detectable levels of hypocretin in those that have type 1 narcolepsy. Since the initial discovery of hypocretin and studies elucidating the various roles it plays in human functioning, further research has been slow and many research questions remain unanswered, thus providing new opportunities for researchers in this area. Currently there are no published studies that compare the expression of symptoms in relation to pain, migraines, headaches and general health and wellbeing amongst people with type 1 and 2 narcolepsy.

Throughout the following sections this review will present the available evidence in these areas and pose questions in relation to the hypothesised theories of hypocretin and its role in pain, migraines, headaches and general health and wellbeing among people with narcolepsy. Understanding the effect of hypocretin in narcolepsy and its association with pain, migraines, headaches and general health and wellbeing may provide knowledge to aid in the development of appropriate treatment for these symptoms and thus improve quality of life.

4.1. Migraine and headaches

Migraines can be described as severe headaches that are accompanied by other symptoms. Other symptoms may include nausea, vomiting, sensitivity to light, sound and or smell. A relationship between sleep, migraines and headaches has been found (Bigal & Hargreaves, 2013). One explanation for this relationship concerns the unusual brain activity occurring in the hypothalamus, where hypocretin is produced, before the onset of a migraine attack. This type of activity only occurred if a migraine was going to follow (Alstadhaug, 2009; Cortelli & Pierangeli, 2007; Moulton, Becerra, Johnson, Burstein, & Borsook, 2014). This was found using positron emission tomography (Alstadhaug, 2009) and functional magnetic resonance imaging (Moulton et al., 2014) of people who were about to experience a migraine, and it continued throughout the migraine attack. Other relevant research has found that migraines and headaches are related to sleep. It is believed that migraines might cause

circadian rhythm disturbances (Solomon, Lipton, & Newman, 1992). It has been found that people who experience migraines show a circadian variation in migraine onset between 6am and 8am and with a decrease between 8 pm and 4 am (Solomon et al., 1992). This observation has also been found in people experiencing a myocardial infarction, platelet aggreability and when plasma cortisol and plasma catecholamines are present (Solomon et al., 1992). Also, changes to sleeping patterns and disturbed sleep can trigger a headache or migraine attack (Kelman & Rains, 2005). Kelman and Rains (2005) collected data using face to face interviews with the use of individually administered questionnaires about participants sleeping habits, migraine and headache diagnoses and other demographic data. They found that participants that slept six hours, who were considered "short sleepers", experienced more frequent severe headaches than participants that slept longer hours. Also, participants that experienced migraines, reported sleeping less hours and experienced more sleep disturbances than participants that did not experience migraines (Kelman & Rains, 2005).

A further study has found a mutation in the HCRT gene, which may make people more susceptible to migraines and cluster-headaches (Rainero et al., 2004, 2011). These findings were obtained by extracting genomic DNA from 109 cluster headache patients, 211 controls (Rainero et al., 2004) and 384 migraine patients and 384 case-controls (Rainero et al., 2011). It could be hypothesised that the gene that produces hypocretin has a mutation in both people with narcolepsy with cataplexy and people who have migraines. However, another study that contained a larger sample size found no association with the HCRT gene (Anttila et al., 2010).

Research has produced conflicting results regarding the association between hypocretin and migraines and/or headaches in people *without* narcolepsy but with low hypocretin levels. It has been found that headaches and migraines are a common symptom experienced amongst people with epilepsy (Syvertsen, Helde, Stovner, & Brodtkorb, 2007), Hashimoto encephalopathy (Huete, Sanchez-del-Rio, & Franch, 2007) and head trauma (Theeler & Erickson, 2009); three conditions which have been found to have lower levels of hypocretin compared to people without a sleep disorder or neurological condition (Castillo et al., 2004; Rejdak et al., 2009, 2001). However, particular care must be taken on this issue with regard to Hashimoto encephalopathy, which has been found to as research has found to mimic the symptoms of a migraine with aura (Huete et al., 2007). Thus it is hard to determine whether a person with Hashimoto is just experiencing the symptoms associated with the neurological condition or are experiencing a migraine attack. This opens up the possibility that having lower levels of hypocretin could be associated with causes of migraines and headaches. However, a causal link must be viewed cautiously, with another study finding that the more anxious the chronic migraine patient was, the lower their hypocretin levels were (Peres et al., 2011).

Research examining migraines and headaches experienced by people *with* narcolepsy is limited and contradictory. One study found that it is common for people with narcolepsy to experience migraines and headaches (Dahmen et al., 2003). Dahmen et al. (2003) administered various questionnaires that assessed migraines, headaches and narcolepsy symptoms to 100 people with narcolepsy and compared the findings amongst the participants within the study. Another study looked at the types of headaches and migraines experienced by people with narcolepsy and found that they did not experience more migraines than healthy participants, but did experience more tension-type headaches (The DMKG Study Group, 2003). This study consisted of 96 narcolepsy participants and 96 age and sex matched control participants. Data collection included interviews, electroencephalography, brain imaging, MSLTs and polysomnography. However, both these studies did not differentiate between people with type 1 or 2 narcolepsy. Dauvilliers et al. (2011) did make this distinction and found that patients who suffered from type 1 narcolepsy did not experience more headaches than non-clinical participants. Their study used face-to-face interviews and questionnaires from 67 people with type 1 narcolepsy and 67 age and sex matched healthy controls. To date, no other studies have looked at the difference in type of migraines and headaches experienced by people with narcolepsy and whether the presence or absence of cataplexy (and therefore presumably hypocretin) may be implicated. Thus, it remains to be determined whether at least some of the headaches and migraines in narcolepsy may be due to a hypocretin deficiency or if it is just a common symptom

experienced amongst people with narcolepsy (Dahmen et al., 2003) and unrelated to hypocretin levels. Accordingly, the following questions are proposed:

> Do people with type 1 narcolepsy experience more migraines and headaches than people with type 2 narcolepsy and healthy controls?
>
> And do people with type 1 narcolepsy experience a different location and type of migraine and headache than people with type 2 narcolepsy and healthy controls?

4.2. Experiencing pain

Research has investigated the symptoms of pain experienced by people with type 1 narcolepsy (Dauvilliers et al., 2011; Ervik et al., 2006). One study collected information using a questionnaire from 77 patients with type 1 narcolepsy regarding their quality of life (Ervik et al., 2006). Another study used face-to-face interviews and questionnaires to collect information from 67 people with type 1 narcolepsy regarding the presence and frequency of pain, narcolepsy symptoms and their quality of life (Dauvilliers et al., 2011). These studies found that pain was more often experienced amongst this population when compared with a healthy sample of participants. It is speculated that hypocretin has analgesic properties (Bingham et al., 2001; Kajiyama et al., 2005) and that this is related to stress-induced analgesia (SIA), the key behavioural component of the 'fight or flight' response. Previous research has suggested that hypocretin regulates SIA, because when hypocretin is low or non-detectable, SIA is not adequately regulated (Bingham et al., 2001; Xie et al., 2008). Therefore, as people with type 1 narcolepsy have low to non-detectable levels of hypocretin, they may be more susceptible to experiencing pain, through a lower pain threshold. Furthermore, the location of pain experienced among people with type 1 narcolepsy in one particular study appears to be consistently reported as in their limbs, such as lower arm or lower leg, whereas people without a disorder of daytime sleepiness reported pain in their back or neck (Dauvilliers et al., 2011). However, these studies did not compare their findings across type 1 and 2 narcolepsy. It is unclear, therefore, whether hypocretin has an effect on the type, severity, and location of pain experienced, or if this is just a common symptom that people with narcolepsy suffer from. That is, sleepiness may, in itself, decrease pain tolerance. However, other studies have found that ongoing sleep disturbances, which causes sleepiness in people, increases spontaneous pain (Smith, Edwards, McCann, & Haythornthwaite, 2007) and increased sensitivity to pain (Chhangani et al., 2009). Therefore, the following question is proposed:

> Do people with type 1 narcolepsy experience different types, severity and location of pain than people with type 2 narcolepsy and healthy controls?

Another factor which may explain the symptoms of pain experienced is the presence of migraines and/or headaches. As mentioned above, people with narcolepsy have been reported to have higher rates of reporting migraines and headaches. A recent study found that people in general who experience frequent migraines and/or headaches are more likely to experience widespread pain (Stuginski-Barbosa, Dach, Bigal, & Speciali, 2012). In relation to applying these findings to people with narcolepsy, it can be argued that because people with narcolepsy may experience headaches and migraines, they are more likely to experience widespread pain. However, this is just a speculative association as no research has looked at whether there is a link between headaches/migraines and widespread pain amongst people with narcolepsy.

4.3. General health and wellbeing

Additionally, the general health and wellbeing of people with narcolepsy has been found to be reduced. People with narcolepsy often display symptoms that are associated with depression (Chellappa & Araújo, 2006), anxiety (Fortuyn et al., 2010) and stress (Berridge, Espana, & Vittoz, 2010; Bruck, 2001). However, it is unclear as to why these symptoms are expressed.

Hypocretin may play a role in the symptoms associated with depression. Recent evidence has shown a link between hypocretin and the dopaminergic pathways (Borgland & Labouèbe, 2010). Dopamine is a neurotransmitter that plays several important roles within the brain and body, including depression (Dailly, Chenu, Renard, & Bourin, 2004). It has been found that when there are low to non-detectable levels of hypocretin, the release of dopamine is decreased, leading to depressive symptoms.

When mice displayed symptoms that were associated with depression, their hypocretin levels in the hippocampal region were reduced (Arendt et al., 2013). This suggests that hypocretin levels may play an active role in the expression of depressive symptoms. On the other hand, other studies suggest that depressive symptoms experienced by people with narcolepsy are independent of hypocretin (Jara, Popp, Zulley, Hajak, & Geisler, 2011; Lindsley & Crawford, 1996). These studies found that people with type 1 and 2 narcolepsy, all experienced symptoms of depression. That is, the level of hypocretin did not make a difference to the level of symptoms experienced with depression. Another study produced results that were unclear as to whether low levels of hypocretin contributed to the depressive symptoms or if the depression was due to suffering from pain (Dauvilliers et al., 2011). When an individual is suffering from chronic pain, their general health and wellbeing, and consequently their psychological wellbeing, are affected (Kim et al., 2015).

The pathology of anxiety and stress experienced by people with narcolepsy is unclear. Studies have concluded that people with narcolepsy suffered more from anxiety, panic attacks (Fortuyn et al., 2010) and stress (Broughton & Broughton, 1994). This was found when comparing people with narcolepsy to normative values (Broughton & Broughton, 1994) and to a healthy case-control age and sex matched comparison group (Fortuyn et al., 2010). Similar results concerning psychosocial wellbeing were found when comparing people with narcolepsy to other illness groups (Bruck, 2001). This study compared the 'mean' total psychosocial adjustment scores of 129 people with type 1 narcolepsy against normative scores of three other illness groups (using the Psychosocial Adjustment to Illness Scale). Bruck (2001) found that people with narcolepsy had more problematic psychosocial adjustment than the cardiac, mixed cancer or diabetes groups. Unfortunately, there appears to be no published research that compares symptoms associated with depression, anxiety and stress between people with type 1 and 2 narcolepsy. In researching this issue it would be important to control for the possible confounding symptoms of pain and migraines/headaches, given the above presented research (albeit not with consistent findings) suggesting that people with type 1 narcolepsy may differ in the degree to which they experience pain and migraines/headaches compared to people with type 2 narcolepsy. Therefore, two further research questions are proposed:

> Is the relationship between levels of pain and symptoms of anxiety and depression stronger in people with type 1 narcolepsy compared with people with type 2 narcolepsy and healthy controls?
>
> Is the relationship between symptoms of migraines/headaches and symptoms of anxiety and depression stronger in people with type 1 narcolepsy compared with people with type 2 narcolepsy and healthy controls?

One study suggested that people who suffer from chronic migraines and who have a higher level of anxiety have significantly lower levels of hypocretin when compared to people who suffer from chronic migraines and who have lower levels of anxiety (Peres et al., 2011). This was the first study that investigated migraine sufferers' hypocretin levels in association with anxiety. It is unclear whether anxiety lowers levels of hypocretin or lower levels of hypocretin contribute to anxiety. It is also unclear whether experiencing migraines and headaches has an effect on symptoms associated with anxiety and depression. Thus a possible relationship between anxiety levels and the presence or absence of cataplexy could usefully be explored, where all groups being compared could experience migraine and/or headache symptoms.

5. Summary and conclusion

Approximately two thirds of people with narcolepsy suffer from cataplexy (Thannickal et al., 2009). The presence of cataplexy in people with narcolepsy has a well-documented tight association with very low or non-detectable levels of the central nervous system neuropeptide, hypocretin (Heier et al., 2007; Savvidou et al., 2013), whereas further studies have shown that levels of hypocretin are normal in people without cataplexy (Silber et al., 2002). There is evidence to suggest that hypocretin has an effect on pain (Dauvilliers et al., 2011), migraines (Dahmen et al., 2003) and headaches (The DMKG Study Group, 2003). However, these studies have not compared these findings with a group of participants with Type 1 and 2 narcolepsy. Currently, there are no studies published to determine whether pain, migraines and headaches are just common symptoms experienced by all people with narcolepsy or whether the presence of the cataplexy symptom (and thus assumed low levels of hypocretin) exacerbates these symptoms. Also, it is unclear whether general health and wellbeing are similarly affected (Dauvilliers et al., 2011). Future research could move in the direction of investigating whether the presence or absence of cataplexy is differentially associated with different types, severity and location of chronic pain; frequency, location and types of migraines and headaches, and general health and wellbeing (including psychological wellbeing) among people with type 1 and 2 narcolepsy. Increased understanding the role of hypocretin in narcolepsy could provide knowledge to aid in the development of better treatments for pain, migraines and headaches among people with narcolepsy and possibly also for people without narcolepsy. Ultimately, this could help improve the quality of life for people with and without narcolepsy.

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