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Medical hypothesis

Cataplexy: 'tonic immobility' rather than 'REM-sleep atonia'?

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Abstract

Background: Cataplexy, a sudden loss of muscle tone in response to strong emotions, is the most specific symptom of narcolepsy. It is currently thought to be due to disturbed rapid eye movement (REM) sleep regulation, and portrayed as REM sleep atonia occurring at the wrong time. However, there are several arguments against including cataplexy in the 'state boundary control' hypothesis. It does not explain why cataplexy is triggered by emotions, and recent studies in narcoleptic dogs showed that REM sleep regulatory mechanisms were in fact intact in these animals.

Methods: We review the literature on the REM sleep dissociation theory, discuss the merits and demerits of the theory, and propose an alternative hypothesis explaining cataplexy.

Results: Cataplexy may represent an atavism (recurrence of an ancestral characteristic) of tonic immobility. Tonic immobility (TI) denotes a condition in which an animal is rendered immobile when faced with danger. Arguments in favor of the TI hypotheses are that it explains the emotional triggering. Furthermore, centers regulating narcolepsy and TI are both located in the lateral hypothalamic area. Finally, several drugs known for their ameliorating effect on cataplexy reduce the frequency and duration of TI in animals.

Conclusion: Cataplexy may be due to a mechanism different from the other clinical symptoms of narcolepsy.

Keywords: Narcolepsy; Cataplexy; Rapid eye movement sleep; Atonia; Tonic immobility; Atavism

1. Introduction

The four cardinal symptoms of narcolepsy are commonly bundled to form a 'tetrad' consisting of excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations and sleep paralysis [1–3]. Fragmented nighttime sleep is often considered to be an integral fifth part of the syndrome [3,4].

The symptoms of narcolepsy are rather diverse in nature. EDS is manifested by the tendency of patients to fall asleep at any moment during the day, although factors that normally increase sleepiness, such as performing boring tasks or having eaten, facilitate this propensity. Hypnagogic hallucinations are vivid dreamlike experiences occurring when patients fall asleep or wake up. In sleep paralysis, patients are frightened to find themselves unable to move a muscle during the transition from waking to sleep or vice versa. Cataplexy refers to attacks of flaccid muscle weakness triggered by a variety of emotions such as humor or anger.

Faced with this set of apparently bizarre and irreconcilable symptoms, researchers have searched for a common pathophysiological ground. EDS and fragmented nighttime sleep can be explained by an inability to sustain any vigilance state: patients, while awake, cannot stay awake, and when asleep, do not stay asleep. Cataplexy, hypnagogic hallucinations and sleep paralysis have been considered as partial manifestations of rapid eye movement (REM) sleep occurring at the wrong time [5,6]. This 'REM sleep dissociation hypothesis' portrays cataplexy and sleep paralysis as aspects of the normal motor inhibition that prevents us from acting out our dreams during REM sleep. In this view hypnagogic hallucinations are seen as dreaming occurring during the waking state. Broughton et al. [7] coined the term 'loss of state boundary control' to provide an integrative explanation of all four symptoms of the narcoleptic tetrad.

Although the mechanism underlying the symptomatology of narcolepsy remained unknown for a long time, tremendous progress has been made in our understanding of the neurobiology of narcolepsy in the last 2 years. A dysfunction of an unexpected duo of neurotransmitters, the hypocretins, was shown to be the paramount cause of narcolepsy in humans, dogs and mice [8–11]. The hypocretins (also known as orexins) are neuropeptides produced by a small number of neurons in the lateral hypothalamic area (LHA)

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[12–14]. The hypocretin neurons have connections virtually throughout the entire neuraxis [15]. This arrangement makes the hypocretin system particularly suitable to orchestrate various body functions, including state boundary control [3].

Although loss of state boundary control is an elegant and convincing explanation for EDS and fragmented nighttime sleep, that part of the theory involving REM sleep dissociation leaves a number of questions unanswered. One of the more obvious shortcomings is that the hypothesis does not in any way address the triggering of cataplexy by emotional stimuli: although dreams may cause emotions, REM sleep itself is not brought on by emotions, so why should emotions evoke REM sleep atonia?

In this article, we discuss the merits and demerits of the dissociation hypothesis to explain cataplexy, and contrast them with a novel hypothesis according to which cataplexy may represent a recurrence (atavism) of the ancestral trait of 'tonic immobility'. Tonic immobility (TI) denotes a condition exhibited by numerous vertebrates, in which an animal is rendered immobile when faced with danger, i.e. because of an emotional trigger [16,17]. The two theories will be compared, focusing on clinical, physiological and neurochemical aspects, and are followed by suggestions for experiments to test the validity of the 'TI hypothesis'.

2. Cataplexy

2.1. Clinical aspects

Cataplectic attacks are triggered by strong emotions, including humor, anger and surprise [3,18]. It is interesting to note that laughter is mentioned as the most effective trigger throughout the literature, although strictly speaking it is not an emotion but a motor act with profound social functions, including the expression of humor or mirth [19]. Similarly, when patients describe the unexpected meeting of an acquaintance evoking cataplexy, the trigger is probably the emotion of surprise raised by the encounter rather than the encounter itself.

Consciousness is preserved during cataplexy, so patients are fully aware of the apprehension and even alarm the attack can cause to bystanders as well as to themselves. Cataplexy is not always complete, and may affect only the muscles of the neck or the knees. Patients are always able to breathe and move their eyes. After a short period, lasting several seconds to a few minutes, the attack stops rather abruptly, and patients can resume their activities.

Cataplexy also forms part of the phenotype of animals with narcolepsy. In the well-known hereditary canine model, cataplexy is typically brought about when animals are confronted with pieces of palatable food, or when playing together [20]. Mice rendered narcoleptic by disrupting the hypocretin gene display cataplexy-like episodes of abrupt motor arrest from which they recover equally suddenly [9,21]. It is not yet clear what the triggers are in these mice.

2.2. Neurophysiology

Several studies describe the neurophysiological features of cataplexy, both in dogs and in man. The electroencephalogram (EEG) during cataplexy shows patterns of normal wakefulness in both species [22–24]. During longer cataplectic attacks, the EEG may gradually show features of REM sleep and patients may report dreaming [25], making it difficult to distinguish cataplexy from REM sleep.

Muscle weakness is due to inhibition of motor neurons at the spinal level, explaining why tendon reflexes are depressed or abolished during cataplexy [23]. In addition, there is a complete depression of the H-reflex, which technique tests the same reflex pathway using electromyography [23].

Cataplexy seems to be associated with autonomic changes. There usually is a marked decrease in heart rate during cataplexy in dogs [26]. Studies in human subjects reported a decrease in blood pressure at the onset of cataplexy, with a compensating tachycardia [27]. A recent experiment using continuous polygraphy in one human patient demonstrated that the majority of cataplectic attacks are accompanied by bradycardia after an initial increase in heart rate [24].

2.3. Neurochemistry and neuropharmacology

The neurochemical basis of cataplexy is complex, with pharmacological studies indicating the involvement of several neurotransmitter systems [28,29]. The canine model for narcolepsy has been invaluable to elucidate the role of the various brain regions and their interaction in the development of cataplexy [28]. Most of the data reviewed below have been derived from experiments in narcoleptic dogs.

Several neuronal populations in the pontine brainstem are crucial in the generation of cataplexy. Based on extensive neuropharmacological and neurochemical experiments, Nishino et al. [28] developed a model for the control of cataplexy in which both monoaminergic and cholinergic systems in the brainstem play a key role. In short, cataplexy is aggravated by cholinergic activation, or deactivation of monoaminergic (most importantly adrenergic) systems [28,30,31]. In humans, there seems to be a similar imbalance between these two neuronal populations. For example, the alpha-1 adrenergic antagonist prazosine severely worsens cataplexy [32,33]. Conversely, the various substances effective in the treatment of cataplexy (such as the tricyclic antidepressants) share the fact that they increase norepinephrine availability [29].

Other brain regions, distinct from the brainstem, are also involved in the modulation of cataplexy. Using local injection experiments, cholinoceptive sites in the basal forebrain/anterior hypothalamus of narcoleptic dogs were shown to be

very important in the modulation of cataplexy [34]. Injections with carbachol, a cholinergic agonist, in this region aggravated cataplexy in a dose-dependent manner and could even induce a *status cataplecticus* [34]. Because acetylcholine release in the basal forebrain is increased during emotional stimulation [35], this region may be involved in the emotional triggering of cataplexy [35,36].

In summary, an imbalance between pontine monoaminergic and cholinergic neuronal populations is thought to underlie the pathophysiology of cataplexy, with the cholinoceptive sites in the basal forebrain as a possible region involved in the emotional trigger [28,30,31,36].

3. REM sleep and the REM-dissociation hypothesis

REM sleep has fascinated clinicians and researchers since its discovery in 1953 [37]. During REM sleep the skeletal musculature is tonically, i.e. continuously paralyzed [30,38]. Superimposed on this paralysis are the so-called phasic phenomena, such as muscle twitches and bursts of eye movements. During REM sleep we experience dreams; more than 80% of people report dreaming when awakened from REM sleep [39].

Normally, REM sleep occurs 90 min after sleep onset, and thereafter recurs at approximately 90-min intervals [39]. In narcolepsy, REM sleep typically occurs rapidly after sleep onset. The discovery of these sleep-onset REM periods (SOREMPs) [40,41] gave rise to the idea that narcolepsy is essentially a disorder of REM sleep generation. Shortly thereafter, the REM sleep dissociation hypothesis took shape, depicting cataplexy, hypnagogic hallucinations and sleep paralysis as partial features of REM sleep occurring during the waking state [5,6]. Cataplexy naturally represented the inadvertent expression of REM sleep atonia in this view. Several observations support the REM-dissociation theory.

3.1. Clinical picture and neurophysiology

During REM sleep, breathing continues and ocular movements occur despite the inhibition of the skeletal musculature [30,38], strongly resembling the pattern of muscle weakness during cataplexy, where the extraocular and respiratory muscles remain functional [25]. In addition, the disappearance of reflexes, including the H-reflex, during cataplexy is paralleled in REM sleep [23].

3.2. Neurochemistry and neuropharmacology

The model for the control of cataplexy, characterized by an imbalance of pontine cholinergic and monoaminergic systems, is strikingly similar to the model of REM sleep regulation [28,30,38]. This neurochemical similarity is corroborated by functional studies measuring the firing rate of neurons in different areas of the brain. Cell groups in the nucleus magnocellularis of the medial medulla, which are activated during REM sleep to induce muscle weakness, discharge at a high rate during cataplexy as well [42]. Likewise, neurons in the locus coeruleus that are inactive during REM sleep cease to discharge during cataplexy [43].

Several compounds that increase adrenergic function are known to reduce the amount of REM sleep. Examples include tricyclic antidepressants, and monoamine oxidase inhibitors [29,44]. These pharmacological effects further illustrate the importance of adrenergic mechanisms in the control of REM sleep.

4. The REM-dissociation theory revisited

The experiments described in the previous paragraph show that cataplexy and REM sleep make use of a common final pathway in the brainstem that generates muscle atonia. However, cataplexy is not necessarily due to a disturbance of REM sleep regulation per se. Although there are several arguments against the REM-dissociation theory, which we will outline here, very few authors have submitted the hypothesis for discussion. In fact, no study directly addressing the question of whether narcolepsy is indeed a disorder of REM sleep regulation was available until the year 2000 (see subsequently) [45].

If a disturbance of REM sleep regulation were the principle cause of narcolepsy, one would anticipate that the other presumed REM-dissociation symptoms (hypnagogic hallucinations and sleep paralysis) would also occur exclusively in the narcoleptic syndrome. This is, however, not the case; both hypnagogic hallucinations and sleep paralysis are common in the general population [46–48]. Furthermore, the symptoms do not even need to occur together in narcolepsy: although the majority of narcoleptic patients experiences cataplexy, the percentage of patients with hypnagogic hallucinations and sleep paralysis is much lower [1,49]. Additionally, there does not seem to be any relation between the severity of cataplexy and the severity of either hypnagogic hallucinations or sleep paralysis (personal observation, G.J. Lammers).

A number of limitations of the REM-dissociation theory pertain to cataplexy directly:

1. Cataplexy is typically triggered by strong emotions. However, emotions such as humor and anger are normally not linked to the onset of REM sleep.
2. The disappearance of the H-reflex during cataplexy has been explained as supporting the REM-dissociation hypothesis because REM sleep is presumed to be the only state in which the reflex is normally inhibited [23,50]. However, we recently showed that this is not the case: the H-reflex disappears during laughter in cataplectic subjects as well as in healthy controls [51,52].
3. The cholinoceptive site in the basal forebrain, where cataplexy can be induced in narcoleptic dogs, is located in the anterior hypothalamus [34], a considerable

distance away from the brainstem regions known to be involved in the regulation of REM sleep [30,34,38]. The involvement of forebrain structures in REM sleep regulation cannot be, however, excluded [53,54].

4. Sulpiride, a dopamine D2/D3 antagonist, significantly reduced cataplexy in narcoleptic dogs but did not cause a reduction in the amount of REM sleep [55]. These findings are in line with studies showing that D2/D3 agonists injected into midbrain dopaminergic nuclei can aggravate cataplexy [56,57], although these regions do not play a role in REM sleep regulation [58].

In a recent article Nishino et al. [45] focused directly on REM sleep control in narcolepsy, using the canine narcolepsy model to study various aspects of sleep regulation. Narcoleptic dogs showed a much more fragmented sleep pattern than normal dogs, although the total time spent in each vigilance state over 24 h did not differ from controls [45]. REM sleep cyclicity shows an ultradian rhythm of about 30 min in dogs [59]. Interestingly, the REM sleep cycle of narcoleptic canines is intact and shows normal intervals [45]. Moreover, during long lasting attacks of cataplexy elicited by carbachol injections in the basal forebrain, bursts of REMs and other phasic REM sleep features occurred only intermittently, following the normal 30 min cycle [45]. In contrast to REM sleep, cataplexy did not show any periodicity, and could be triggered at any time of the day. From these data, the authors concluded that narcolepsy should not be seen as a disorder of REM sleep regulation, and that cataplexy is likely to be a pathological event distinct from a REM-sleep phenomenon [45].

We agree with Nishino et al.'s [45] view that narcolepsy is explained by a combination of failure to sustain vigilance states and cataplexy. In light of the arguments described previously, cataplexy does not seem to be governed by REM sleep regulatory mechanisms. However, no mechanism explaining the nature of cataplexy has been put forward. We extend this dualistic view by proposing that cataplexy is an atavistic expression of TI.

5. Tonic immobility

TI describes a response pattern characterized by severe motor inhibition when an animal faces grave danger, such as being held by the jaws of a predator [16,17]. Unfortunately, the nomenclature of this reaction pattern is highly confusing, with numerous terms, such as animal hypnosis, immobility reflex, 'Totstellreflex', feigning death, playing dead and fright paralysis, being used throughout the literature [60]. TI is well documented across the animal kingdom, but has been described particularly often in pigs, opossums, chickens, and sharks [17].

5.1. Features

TI has the properties of a reflex: although complex, it is a specific, relatively stereotyped involuntary response to specific stimuli [16]. TI has been widely investigated, and several paradigms have been developed to elicit the reflex, one of which is to suddenly place an animal on its back and restrain it in that position. The unlucky animal will become immobile for a certain period, after which it will abruptly revert to its normal mobile state [17]. This technique has been used to select for breeding pigs that are less sensitive to environmental stress [61]. In scientific research, this method makes it possible to quantify the effects of pharmacological interventions, for example, by measuring the duration of induced TI [62].

Animals are fully conscious during TI, and several observations showed that they keep a check on their surroundings during the period of immobility. TI in chickens lasted longer in situations when there was no chance of escape compared to those where such chances were available [63]. During TI, opossums reacted to the approach of a dog with changes in heart rate and twitching of the ears [64].

There are surprisingly few systematic studies evaluating muscle tone during TI. Klemm [65] described a 'waxy flexibility' in which there may be muscle flaccidity. However, animals sometimes assume specific body postures during TI, indicating that some muscles remain functional. Muscle tone may also change. In fact, TI may begin with 'a great deal of muscle tone, culminating in marked flaccidity' [65].

5.2. Neurophysiology

Studies in various animal models showed that the EEG during TI cannot be distinguished from the normal waking EEG [16,64]. However, animals could fall asleep in laboratory situations during prolonged immobility [16]. In rabbits, easily susceptible to TI, there is a depression of both mono- and poly-synaptic reflexes, associated with a flaccid paralysis [66]. Based on both the clinical features of TI and its neurophysiological findings, it has been proposed that the brainstem systems involved in the generation of REM sleep atonia are used as the effector mechanism in TI as well [16,67,68]. TI does not merely consist of motor inhibition, but is also associated with autonomic responses. During TI blood pressure decreases and bradycardia usually occurs after an initial increase in heart rate [17].

5.3. Neurochemistry and neuropharmacology

The tendency to develop TI, and the severity of the immobility, are influenced by a great number of systems [65]. Many studies are hampered by differences in the classification of immobility responses and effect parameters, but results suggest that virtually any neurotransmitter may be involved in the regulation of TI [65]. Several more recent studies focused on the cholinergic system, finding that anticholinergics reduced and cholinomimetics increased the severity of TI in a number of species, including birds, guinea pigs and toads [69–71]. Moreover, experiments using localized injections of carbachol demonstrated that cholinergic

neuronal populations in the anterior hypothalamus and basal midbrain are very important in the induction of TI [71,72]. Interestingly, other parts of the hypothalamus, including the LHA, are involved in the modulation of TI as well [72,73].

6. Cataplexy as an atavistic expression of TI

Although it is hard to be certain, TI has not been reported to occur in normal, healthy humans. Certainly, the phrase 'to be paralyzed with fear' suggests that a similar state may exist in man. It is difficult to decide whether the immobility to which this term refers is brought about by a reflex, as in animals, or by an inability to decide on an action under conditions of life-threatening danger. TI is not a likely part of the behavioral repertoire of other primates since it has never been described. Klemm [16] suggested that the neocortex has an inhibiting influence on TI and that its expression diminishes as the neocortex gets larger. This, however, does not mean that the underlying reflex mechanism has been eliminated from our nervous systems.

There are numerous examples of traits not normally exhibited but cropping up occasionally, evidencing that the trait was dormant rather than absent [74]. Such atavisms – reappearances of ancestral characteristics – include the presence of a tail or excessive body hair in humans. A specific example of an atavistic form of TI is found in the 'Arkansas Nervous Pointer Dog' [75]. Although dogs do not normally exhibit TI, these Pointer dogs exhibit a range of abnormal behavior patterns, including reacting with TI to the presence of humans [75].

We surmise that cataplexy represents an atavistic form of TI, based on the following arguments:

1. Emotions form an important part of the triggering mechanism in TI [16,17]. Considering the situations in which TI occurs, fear seems to be the major emotional trigger in animals. Cataplexy in humans is typically brought about by other emotions, particularly humor [18]. Although fear is not typically reported as a trigger by patients, negative emotions such as anger and embarrassment have been reported [18], and there have been no studies specifically addressing this question. Cataplexy is quite easily evoked in canines by playing and eating or anticipating tasty food [20], also suggesting that various emotions play a role. We propose that an intense emotion, or its anticipation, forms the actual trigger, with the specific type of emotion depending on the species. With regard to the role of laughter, it is important to note that humans are among the few species[1] that overtly laugh, making it virtually impossible to determine if humor is able to trigger TI or cataplexy in animals.
2. Both TI and cataplexy make use of the brainstem regions responsible for REM sleep atonia as a final common pathway to induce the spinal inhibition of motor neurons [16,30,42,67,68]. However, there are many fewer phasic REM phenomena, such as bursts of eye movements and muscle twitches, during TI and cataplexy compared to REM sleep [45,67,68].
3. TI and cataplexy are both associated with bradycardia in the majority of cases [17,24,26].
4. It is tantalizing to speculate that the hypocretin system is involved in the suppression of TI in primates and that, when compromised, it gives way to abnormal expressions of TI. The hypothalamus, including the LHA, is an important brain region involved in the generation and modulation of TI [71,72,73]. We now know that the LHA, where the hypocretin system resides, is the primary brain region responsible for the development of narcolepsy with cataplexy [3,76].
5. Several studies showed the presence of a cholinoceptive site in the basal forebrain involved in the triggering of both TI and cataplexy. Carbachol injections in the anterior hypothalamus of narcoleptic dogs greatly increase the frequency and severity of cataplexy [34]. Likewise, carbachol injections in the anterior hypothalamus of the guinea pig and the basal midbrain of the toad have an aggravating effect on TI [71,72].
6. Tricyclic antidepressants and monoamine oxidase inhibitors are known for their ameliorating effect on cataplexy [29]. Both imipramine (a tricyclic antidepressant) and iproniazid (a MAO inhibitor) greatly reduce the duration of TI [77,78].

7. Conclusions and further consequences

The prevailing view, which holds that all symptoms of narcolepsy are explained by a loss of state boundary control [7], now needs revision [45]. It is necessary to adopt a combination of at least two separate mechanisms to fully describe the pathophysiology of narcolepsy. Although loss of state boundary control may still be an adequate explanation for EDS and fragmented nighttime sleep, cataplexy cannot be fully described by this concept because the sites and mechanisms triggering cataplexy and REM sleep appear different [45]. An attractive alternative would be to portray cataplexy as an atavistic expression of TI.

One can think of several experiments that may shed more light on the cause of cataplexy and the possible involvement of TI in particular. It will be necessary to obtain more detailed information on muscle tone during TI in various animals. In addition, studying spinal mechanisms of motor inhibition during TI in more detail may provide profound insight in the descending pathways involved.

The hypocretin system is an alluring candidate for regulation of TI. The hypocretin neurons may directly suppress brain areas involved in the initiation of TI, or act as a stabilizing system on brain stem areas responsible for motor

[1] Man is not the only laughing species; chimpanzees, gorillas, orangutans, and perhaps other primates are believed to laugh as well [19].

inhibition, preventing the occurrence of TI/cataplexy in healthy people. This idea is supported by the fact that while the vast majority of patients with cataplexy lack hypocretin-1 in their spinal fluid, narcoleptic patients without cataplexy typically show normal hypocretin levels [79], indicating that the mechanisms of cataplexy and the other symptoms of narcolepsy are quite dissimilar. Neurophysiological and other functional studies comparing these two groups may provide specific knowledge on the origins of cataplexy. Furthermore, the narcoleptic animal models could be very useful to obtain more knowledge on the possible role of the hypocretin system in the modulation of TI. For example, narcoleptic hypocretin knockout mice [9] might display an aggravated form of TI.

Compounds with a beneficial effect on cataplexy, such as the tricyclic antidepressants, should be evaluated in more detail for an effect on TI. Conversely, substances known to aggravate cataplexy, such as alpha-1 antagonists, may have a similar effect on TI. Measuring the effect of hypocretin administration on the frequency or severity of TI in various animals is another experiment that could easily be performed.

Cataplexy remains a fascinating symptom, showing complex interactions between systems involving emotions and those subserving motor control. Incorporating knowledge of the mechanisms regulating REM sleep, cataplexy and TI will be very important to further understand these diverse but related phenomena.

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