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Review article

Hypothetical Radiological Findings in Dogs and Cats Suffering from Insomnia [1]

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Abstract

Sleep is a vital body function, regulating several biological phenomena. Deprivation studies are one of the ways used to examine the physiological functions and the regulation of the sleep. Sleep deprivation is a stressor, and its' effects depend on an individual's prior sleep deficit and distribution during the day. Sleep deprivation can be partial, total, acute, or chronic or specifically focused on one of the sleep phases. Sleep deprivation affects a large spectrum of vital systems such as thermoregulation, energy and mineral balance, and immunofunction. Based on the fact that sleep is a very important process for the normal development of many metabolic pathways, it is logical to think that insomnia has serious organism consequences. Functional irregularities of different organs are always reflected in structural changes that can be identified with imaging techniques. Imaging methods can also help identify problems of animals insomnia.

Keywords: Radiology, Diagnosis, Insomnia, Sleep, Biology.

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INTRODUCTION

Definition of sleep, sleep architecture and sleep profiles

We all understand what it means to be asleep, but it is not always obvious whether observed animals are experiencing the same state. Sleep must be distinguished from circadian changes in alertness controlled by the suprachiasmatic nucleus and other body clocks. Most animals need to adjust their activity to optimal conditions of prey availability, predator threat, sexual opportunities, temperature and other variables affecting survival that vary with time of day. Adequate rest and sleep is essential for the welfare of young growing animals (Rechtschaffen, 1998; Everson, 1995; Siegel, 2005). Sleep regulates the secretion of several hormones, such as GH and glucocorticoids (Steiger, 2002), and is essential for brain development (Mirmiran,1986; Morrissey et al., 2004; Siegel, 2005). Defines mammalian sleep as an individual that sustains quiescence in a species-specific posture accompanied by reduced responsiveness to external stimuli, has a quick reversibility to the wakeful condition and characteristic changes in the electroencephalogram (Zepelin et al., 2005). The behavioural criteria consist of a lack of mobility or slight mobility, slow eye movements, characteristic specifies-specific sleeping posture, reduced response to external stimulation, increased reaction time, elevated arousal threshold, an impaired cognitive function and a reversible unconscious state. Electrophysiologically sleep is split into two main phases: rapid eye movement sleep (REM), also called a paradoxical sleep, or active sleep and non-rapid eye movement sleep (NREM), also called quiet sleep, orthodoxical sleep, or slow wave sleep (SWS). In principal, the smaller the animal and the northern it lives, the shorter the daily sleeping duration and the shorter the REM-phases. The stimulus threshold to wake up from REM-sleep is higher than that of NREM, and thus a long REM-sleep period can be a threat to survival for prey species other than those rodents species that sleep in nests (Allison et al., 1976; Tobler, 1995). Primates often exhibit a mono- or biphasic sleeping rhythm while several other species have a polyphasic rhythm, sleeping all over the day. Typical examples of polyphasic short sleepers are our domestic ruminant species, such as cattle, sheep, and goats. The sleep cycle consists of one or several REM and NREM phases. The cycle length is species-specific. Sleep cycle lengths are short in farm animals, as in several prey animal species. Total daily sleeping duration also varies between species. These differences between species depend on several factors, such as time spent eating, and available food sources, digestion and rumination, and ecological niche (Allison et al., 1976; Elgar et al., 1988;). Grazing animals, for example are assumed to sleep less, as they need more time to consume large amounts of low- calorie foods (Siegel, 2005). In mature mammals and birds, the sleep phase usually starts with NREM and deepens during the REM phase (Zepelin et al., 2005). The young of many terrestrial mammalian species sleep more and have more REM sleep than do older animals (Siegel, 2005). Sleep is essential for brain development, and REM sleep is connected to the early developmental phase (Mirmiran, 1986; Morrissey et al., 2004). Young animals have also higher need for energy conservation acquired through sleep.

Precocial young mammals, such as bovine calves, are suggested to spend proportionally less in REM sleep from their total sleep time than do young altricial mammals (Siegel, 2005).

Functions of the different sleep phases and effects of deprivation

Sleep is a vital body function, regulating several biological phenomena. Many theories have been presented to explain the function of sleep and sleep phases. Most theories assume that sleep serves the same functions for all animal species (Siegel, 2005). Deprivation studies are one of the ways used to examine the physiological functions and the regulation of the sleep. Sleep deprivation is a stressor, and its' effects depend on an individual's prior sleep deficit and distribution during the day. Sleep deprivation can be partial, total, acute, or chronic or specifically focused on one of the sleep phases. Sleep deprivation affects a large spectrum of vital systems such as thermoregulation, energy and mineral balance, and immunofunction (Bonnet, 2005). If sleep loss is chronic, depriving individual animal totally from sleep or selectively from REM or NREM sleep, experimental animals will die within a month due to infections or metabolic disorders. Hormones, which are dependent on sleep, loose their secretion rhythm. Several sleep-related hormonal secretions, such as GH and prolactin, diminish, when sleep is deprived. The body temperature decreases before an individual falls asleep, but during sleep deprivation, the body temperature remains around the normal level (Bonnet, 2005). During NREM sleep, body metabolism slows, body temperature decreases, and oxygen consumption diminishes, so that energy is conserved (Shapiro et al., 1993). Brain glycogen storage is restored during NREM sleep (Benington et al., 1995) and anabolic processes accelerate (Shapiro et al., 1993). NREM sleep may also play a central role in neurogenesis; REM sleep occurs proportionally and absolutely more during early development, and secures neuronal development (Siegel, 2005). Biological rhythms, such as hormonal fluctuation and rest-activity or sleep rhythms, are generated by an internal system. Biological rhythms are classified as circadian, with a cycle of approximately 24-hours, and ultradian, with a cycle less than 24 hours. The main regulator, pacemaker, is in the suprachiasmatic nuclei (SCN). The SCN is situated in the hypothalamus, just directly above the optic chiasm (Buijs et al., 2003). The suprachiasmatic nucleuos functions already in fetuses such as in lambs (Yellon et al., 1987). The main regulators for the SCN are external light and feeding. Other factors that synchronize the circadian system are, for example, nutrition, hormone feed-back mechanisms, activity, and social cues (Buijs et al., 2003). Sleep onset stimulates GH secretion, but the hormones of the somatotrophic axis are also involved in sleep regulation in a complex way. GHRH, for example, stimulates slow wave sleep and slow wave activity, and GH increases REM sleep. The secretion of GH increases during sleep independent of the circadian sleeping cycle, and sleep deprivation diminishes the GH release. In humans, however, a day time GH secretion increases after one night of sleep deprivation, thus partly compensating the loss.

Cytokines are proteins produced by leukocytes and other cells functioning as intracerebral mediators that may play an important role in immune and sleep regulation1. Several cytokines (*e.g.*,

interleukin or IL, interferon alpha or IF-α and tumour necrosis factor or TNF) have been shown to promote sleep (Kapsimalis et al., 2008). There are however, other sleep-promoting substances called sleep factors which increase in concentration during prolonged wakefulness or during infection and enhancing sleep. These factors include delta sleep-inducing peptides, muramyl peptides, cholecystokinin, arginine vasotocin, vasoactive intestinal peptide, growth hormone-releasing hormone (GHRH), somatostatin, prostaglandin D2, and adenosine. There is evidence that cytokines play an important role in the pathogenesis of excessive daytime sleepiness (EDS) in a variety of sleep disorders and in sleep deprivation. Increased production of pro-inflammatory cytokines (IL-6 and TNF-α) have been noted during sleep deprivation causing excessive sleepiness. Viral or bacterial infections causing EDS and increased NREM sleep are associated with increased production of TNF-α and IL-B). Increased sleepiness and disturbed sleep in other inflammatory disorders such as HIV infection and rheumatoid arthritis are associated with increased amounts of circulating TNF-α. Several authors suggested that excessive sleepiness in obstructive sleep apnoea syndrome, narcolepsy, insomnia or idiopathic hypersomnia may be mediated by cytokines such as IL-6, TNF-α . The neuroanatomical substrates of REM and NREM sleep and wakefulness are located in separate parts of the central nervous system5. There are no discrete sleep-wake promoting centers but these states are produced by changes in the interconnecting neuronal systems modulated by neurotransmitters and neuromodulators. Insomnia is the most common sleep disorder affecting the population and is the most common disease encountered in the practice of sleep medicine. Insomniacs complain of difficulty initiating and maintaining sleep, including early morning awakening and non-restorative sleep occurring 3-4 times per week persisting for more than a month and associated with an impairment of daytime function. Acute insomnia may be associated with an identifiable stressful situation. Most cases of insomnia are chronic and co-morbid with other conditions which include psychiatric, medical and neurological disorders (Rechtschaffen, 1998).

The true function of sleep is still being discussed, but sleep undoubtedly affects the endocrine and metabolic systems and the immune function (Rechtschaffen et al., 1983; Bergmann et al., 1989).

Total sleep deprivation in animals

The first report on the total chronic sleep deprivation in rats dates back to 1962 (Bergmann et al., 1989). The animals were kept awake for 27 days, which led to aggressive behaviour, decreased body mass gain and impairment of the startle response. The most detailed analysis of sleep deprivation was based on data deriving from well designed, several-year experiments conducted by Bergmann and Rechtschaffen (Webb, 1962; Everson et al., 1989). The experiments were performed using the diskover-water method, with a rat being placed on a disk over a layer of water, and a polysomnograph signal setting the disk into motion whenever an initiation of sleep was recorded (Cirelli et al., 1999). The sleep deprivation obtained using this procedure made up 70–90% of the experiment time and led to the death

of the animals within 2–3 weeks. In the course of the experiment, weight loss was observed despite an increased food intake, as well as pathological skin reactions on the tail and paws and a bad condition of the fur. Initially, body temperature was elevated, but it decreased during the period preceding death. Plasma levels of the thyroid hormones decreased significantly and heart rate increased. At the same time, no stress symptoms, such as stomach ulcers, elevated ACTH or corticosterone levels, or decreased metabolic rate, could be observed during the experiment (Everson et al., 1989a; Cirrelli et al., 1999). Rats died within 11–32 days (16–21 days on average) from the onset of deprivation, a period comparable to that of food deprivation with lethal effects (17–19 days). However, histopathological findings did not reveal any cause of death (28–30). The animals which survived acute deprivation (that were eventually allowed to sleep) showed a dramatic compensatory increase in the REM sleep (Lyamin et al., 2005). The other symptoms subsided within 24 hours, which indicates that the sleep deprivation did not exert destructive effects either on the cells, the neurons or the vital organs. Nonetheless, a complete recovery of the pre-deprivation levels of the particular sleep stages, or of the heart rate and body temperature, lasted several days (Marinesco et al., 1999; Lyamin et al., 2005). An interesting exception to the rule can be observed among marine mammals: despite the periodic, significant sleep restriction, they do not experience the recovery sleep that would be a typical reaction to prolonged wakefulness, as well as to 4 NREM or REM sleep deficiency, in terrestrial mammals. The seals, for example, when staying in the ocean, can function well for several weeks despite the fact that they exhibit a considerably low duration of the REM sleep. Their sleep architecture changes immediately after they come back to the land. Unihemispheric slow-wave sleep (characteristic of dolphins and whales) is replaced by alternate NREM and REM phases. The sleep time typical for terrestrial conditions is immediately restored, and no symptoms of developing the recovery sleep can be seen (Rampin et al., 1991). Similarly, no rebound sleep occurs in infant dolphins and their mothers who refrain from sleeping throughout the period from the delivery till the youngsters achieve some self-sufficiency, which can last several weeks (Newman et al., 2008). The ability to withstand sleep deprivation is dependent on the species-related natural sleep characteristics regarding the duration and quality of sleep. For instance, large ungulate herbivores have a short, shallow and intermittent sleep, while predators usually sleep long and deeply. The relationship between sleep deprivation and the level of stress has not been fully explained, although the latter may have a varying influence on the compensation for sleep deficits. In a study reporting on wakefulness maintained through immobilization for 0.5 to 4 hours, the recovery sleep became significantly shorter when the immobilization period reached its maximal duration (Siegel, 2008). Two-hour immobilization repeated on the consecutive days of the experiment produced similar effects. However a single 2-hour immobilization resulted in an 92% increase in paradoxical sleep within the following 10 hours, whereas a 2-hour wakefulness, maintained using standard methods (disk or gentle handling), did not significantly affect the sleep that followed (Rechtschaffen et al., 2002). Rats appear to be particularly vulnerable to sleep deprivation enforced using the moving disk method, since in other animals (pigeons), the changes

observed after 24–29 days of this procedure were not as severe as in rats (Newman et al., 2008). Other deprivation procedures were not lethal either to rats or other laboratory animals although this may have been due to the significantly shorter periods of deprivation under other experimental conditions or to the difficulties in achieving total sleep deprivation. In animal experiments, sleep deprivation induced an increased rate of systemic metabolism, which led to reduced body mass despite an increased food intake, even if the animals were provided with food that was rich in proteins and calories. Both in the total and selective deprivation of REM sleep in rats, the plasma concentrations of the thyroid hormones, mainly thyroxine and triiodothyronine, decreased considerably.

Conclusion

Based on the fact that sleep is a very important process for the normal development of many metabolic pathways, it is logical to think that insomnia has serious organism consequences. Functional irregularities of different organs are always reflected in structural changes that can be identified with imaging techniques. We think that there are many pathological and nonpathological conditions that provoke sleeplessness in dogs and cats. Imaging methods can also help identify problems of animal fatigue. To concretize these hypotheses, extensive studies are needed.

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