Muscle Atonia Is Triggered by Cholinergic Stimulation of the Basal Forebrain: Implication for the Pathophysiology of Canine Narcolepsy

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Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and rapid eye movement (REM) sleep-related symptoms, such as cataplexy. The exact pathophysiology underlying the disease is unknown but may involve central cholinergic systems. It is known that the brainstem cholinergic system is activated during REM sleep. Furthermore, REM sleep and REM sleep atonia similar to cataplexy can be triggered in normal and narcoleptic dogs by stimulating cholinergic receptors within the pontine brainstem. The pontine cholinergic system is, therefore, likely to play a role in triggering cataplexy and other REM-related abnormalities seen in narcolepsy. The other cholinergic system that could be involved in the pathophysiology of narcolepsy is located in the basal forebrain (BF). This system sends projections to the entire cerebral cortex. Since acetylcholine release in the cortex is increased both during REM and wake, the basal cortical cholinergic system is believed to be involved in cortical desynchrony. In the current study, we analyzed the effect of cholinergic compounds injected into the forebrain structures of narcoleptic and control dogs. We found that carbachol (a cholinergic agonist) injected into the BF triggers cataplexy in narcoleptic dogs while it increases wakefulness in control dogs. Much higher doses of carbachol bilaterally injected in the BF were, however, shown to trigger muscle atonia even in control dogs. These results suggest that a cholinergic site in the BF is critically implicated in triggering muscle atonia and cataplexy. Together with similar results previously obtained in the pontine brainstem, it appears that a widespread hypersensitivity to cholinergic stimulation may be central to the pathophysiology of canine narcolepsy. Furthermore, hypersensitivity in the BF, an area anatomically connected with the limbic system, would explain why emotional excitation, which is usually an alerting stimulus in normals, triggers cataplexy in narcoleptic dogs.

[Key words: narcolepsy, cataplexy, REM sleep, cholinergic system, ACh, basal forebrain]

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Human narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, rapid eye movement (REM) sleep at sleep onset, and dissociated REM sleep processes such as cataplexy (attacks of flaccid muscle paralysis triggered by emotional excitation) (Daniels, 1934; Guilleminault et al., 1974; Guilleminault, 1976). Canine narcolepsy is a naturally occurring animal model that presents behavioral, pharmacological, and electrophysiological similarities to the human disorder (Mitler et al., 1974; Baker and Dement, 1985; Mignot et al., 1992; Nishino et al., 1993, 1994). No consistent histopathological finding has been reported in canine and idiopathic human narcolepsy (Mitler et al., 1974; Baker et al., 1982; Erlich and Itabashi, 1986; Al-drich et al., 1994). This suggests that the pathophysiology of narcolepsy involves minute abnormalities of the neurochemical mechanisms regulating sleep rather than a localized lesion or an obvious developmental abnormality in the CNS.

There is compelling evidence that the brainstem cholinergic system is central to the control of REM sleep. The brainstem cholinergic neurons originating in the mesopontine tegmentum (MPT) [lateral dorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT)] send ascending projections to various forebrain structures, such as the thalamus and hypothalamus (Satoh and Fibiger, 1986; Woolf and Butter, 1986; Hallanger and Wainer, 1988; Semb and Fibiger, 1989), as well as a descending projection to the pontine and medullary reticular formation (Mitani et al., 1988; Rye et al., 1988; Shiromani et al., 1988). Injection of cholinomimetic agents into the medial-PRF (mPRF) in cats induces REM sleep-like or cataplexy-like states, depending on the site and volume of the injection (George et al., 1964; Mitler and Dement, 1974; Baghdoyan et al., 1984; Valazquez-Moz researching et al., 1989). The putative cholinergic REM sleep on neurons have been identified in the MPT (Sakai, 1988; El Mansari et al., 1989; Steriade et al., 1990; Kayama et al., 1992). Furthermore, acetylcholine (ACh) release in the dorsal tegmental field in cats is known to increase during REM sleep (Kodama et al., 1990).

Cataplexy and REM sleep are likely to be regulated by similar brainstem cholinergic mechanisms. Using the canine model of narcolepsy, we have recently demonstrated that local perfusion of a cholinergic agonist, carbachol, into the mPRF induces status cataplecticus (Reid et al., 1994b), and that ACh release in the mPRF increases during cataplexy (Reid et al., 1994c). Narcoleptic dogs are more sensitive to cholinergic stimulation than normal dogs, as lower doses of carbachol are necessary to induce muscle atonia in these animals (Reid et al., 1994b). This
result, consistent with the previous report that muscarinic receptors in the pontine brainstem are upregulated in narcoleptic dogs (Boehme et al., 1984; Kilduff et al., 1986), suggests that cholinergic hypersensitivity in the mPRF is a critical element in the pathophysiology of canine narcolepsy.

Another cholinergic system that could be involved in the pathophysiology of narcolepsy is the basal forebrain (BF) cholinergic system (nucleus basalis, substantia innominata, diagonal band, and medial septum). This system not only sends projections to the limbic and thalamic systems, but also to the entire cerebral cortex (Divac, 1975; Woolf et al., 1986; Semba and Fibiger, 1989; Semba et al., 1989). This contrasts with MPT projections to the cortex, which innervate only the medial prefrontal lobe (Vincent et al., 1983; Satoh and Fibiger, 1986). The BF cholinergic system may, therefore, be more directly involved in controlling cortical desynchrony during wake and REM sleep (see, Cesamenti et al., 1986; Buzsáki et al., 1988; Sakai et al., 1990; Baghdoyan et al., 1993; Stewart et al., 1984). ACh release in the cortex increases during REM sleep as well as during wake (Kanai and Szerb, 1965; Jasper and Tesier, 1971). These results suggest that the BF cholinergic system could complement MPT cholinergic projections to the thalamus and their well-established function of gating thalamocortical activity (Steriade et al., 1990).

We hypothesized that not only the pontine but also the BF cholinergic systems are involved in narcolepsy. This would explain why narcoleptic subjects show dissociated REM sleep manifestations (REM sleep atonia-like state during wakefulness). In order to explore this possibility, we injected cholinergic compounds into several forebrain structures in both narcoleptic and control dogs and assessed their effects on cataplexy, sleep, and wakefulness.

Materials and Methods

Animals. Six genetically narcoleptic (four males and two females) and three control (three males) Dobermans from the Stanford University Narcoleptic Canine Colony were included in this study. All dogs were housed in individual stainless steel cages (100 × 180 cm²), and all experiments were carried out in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals. Dogs were fed daily at 9:00 A.M. and exposed to a 12 hr light:dark cycle (lights on at 7:00 A.M. and off at 7:00 P.M.). The mean ages of the six narcoleptic dogs and three control dogs were 3.1 ± 0.9 years and 2.6 ± 4.8 years (mean ± SEM), respectively.

Implantation of guide cannulae and electrodes for polygraphic recordings. All surgical procedure were done aseptically. Following preoperative treatment with atropine (0.04 mg/kg, i.v.), the animal was anesthetized with pentobarbital (30 mg/kg, i.v.), Isoflurane inhalant (2% air mixture) was then used to maintain anesthesia. Electrodes for EEG, EOG and EMG recordings were originally prepared on each experimental day.

Microinjections, cataplexy testings, and sleep recordings. The animals were allowed to recover for 3 weeks after surgery before beginning drug injection trials. For each trial, the head of the animal was restrained throughout the injection procedure (for 6–8 min). The styletl was removed, and a 27-gauge needle attached by polyethylene tubing to a 5 µl Hamilton syringe was inserted into the guide cannula. The length of the microinjection needle was previously calculated for each target. The injection needle was slowly lowered to the target below the cortical dura. One microliter or 0.25 µl of saline or saline containing the active drug was injected into the structure over 2 min between 10:00 and 11:00 A.M. The needle was kept in place for 3 min after drug injection and then removed from the guide cannula. The flow in the injection system was tested to confirm that the solution had been delivered.

For each dog, one or two cannulae were placed in each hemisphere to target the BF sites. The cannulae were then cemented to the skull and maintained with a stylet. The implantation coordinates were as guide cannulae, and the tips of the cannulae were placed on the surface of the cortical dura. The cannulae were then cemented to the skull and maintained with a stylet. The implantation coordinates were, for BF, AP 29.0–31.0, L 3.0–5.0, H 8.0 (AP = anterior-posterior, L = lateral, H = height from the stereotaxic zero); caudal BF-I, AP 27.0, L 5.0, H 8.0; caudal BF-2, AP 25.0, L 4.0, H 8.0, and amygdala, AP 21.0, L 13.0, H 9.0. A detailed description of the surgical technique has previously been published (Reid et al., 1994a,b).

Histological verification of the sites of injection. All the animals were eventually sacrificed to verify injection sites and to map both adjacent cholinergic cell groups, and the projections of the injection site (data will be reported elsewhere). Cholecystokinin B subunit (CtB) (0.1 µl of 1% solution in distilled water, List Biological Lab., Campbell, CA) was injected into the BF site 14 hr before the perfusion of the brain. Animals were deeply anesthetized with pentobarbital (30 mg/kg, i.v.) and the brain was perfused through the ascending aorta, first with saline containing 0.1% heparin, then with ice-cooled fixative in 0.1 M PBS (pH 7.4), containing 4% paraformaldehyde, 0.1% glutaraldehyde, and 0.2% picric acid. Immunohistochemical detection of CtB was then carried out according to the procedure described by Luppi et al. (1990). The CtB-pretreated sections were then double stained for the cholinergic markers using ChAT immunohistochemistry. Briefly, the
Carbachol (and carbachol conjugated with microspheres) injection in the BF increases cataplexy in narcoleptic dogs. Carbachol, carbachol conjugated with microspheres (10 nmol/l μl or 0.25 μl) or saline (1 μl) was injected unilaterally into the BF of five narcoleptic dogs. Time course effects of the compounds on cataplexy were assessed by the Food Elicited Cataplexy Test (see Materials and Methods). Carbachol and carbachol microspheres injection significantly aggravated cataplexy with a short latency.

Slide-mounted sections (30 μm thick) were incubated for 3-4 d at 4°C in anti-ChAT monoclonal antibody (1 μg/ml, Boehringer Mannheim, Indianapolis, IN) and then rinsed three times for 15 min in PBS-Triton and incubated for 90 min at room temperature in biotinylated anti-rat IgG (1:2000, Vector Lab., Burlingame, CA). This was followed by three 15 min rinses in PBS-Triton and by a 90 min incubation in ABC-HRP complex (1:500-1000, Vector Lab.). After three additional 15 min rinses in PBS-Triton, sections were reacted with 0.02% 3,3'-diaminobenzidine-4 HCl (DAB, Sigma, St. Louis, MO) containing 0.003% hydrogen peroxide. Sections were dehydrated in ethanol, cleaned in xylene, and coverslipped with permount for microscopic examination.

Data analysis. The significance of the time course effects of drugs on cataplexy was assessed using a repeated-measures ANOVA. The significance of drug effects on each sleep parameter was assessed using a paired samples t test. All computation were performed using a personal computer software package (Systat Inc., Evanston, IL).

Results

Unilateral carbachol (10 nmol) injections into the BF significantly aggravated the cataplexy of narcoleptic dogs, leading to status cataplepticus in most cases [carbachol vs saline, F(4,32) = 19.1, p < 0.01, a repeated measures ANOVA with a grouping factor (time course X session)] (Fig. 1). Polygraphic recordings confirmed that carbachol induced long-lasting muscle atonia with desynchronized EEG similar to spontaneous cataplexy (Fig. 2). In addition, the effect of carbachol conjugated with latex microspheres (0.01-0.2 μm) (provided by Dr. Quattrochi, see Quattrochi et al., 1989) was examined, and this preparation (10 nmol of carbachol) was also found to aggravate cataplexy [carbachol-microsphere vs saline, F(4,32) = 20.5, p < 0.01 (time course X session)] with the same latency and potency as the free carbachol injections [carbachol vs carbachol-microsphere, F(4,32) = 0.94, DF = 4.32, p = 0.98 (time course X session)] (Fig. 1). Free carbachol (10 nmol) injected into the caudal BF-1 site (2 mm caudal to the BF site, see Materials and Methods) of the narcoleptic dogs significantly aggravated cataplexy [F(4,16) = 3.61, p < 0.05, a repeated measures ANOVA], while car-
Badgoyan et al. (Badgoyan et al., 1993) further reported that injections of carbachol into the BF significantly reduced cataplexy. Physostigmine, a cholinesterase inhibitor, did not aggravate cataplexy, while McN-434, an M1 agonist, had no effect on cataplexy. Bilateral injection of atropine significantly reduced cataplexy. Carbachol was also injected into two other sites in the caudal BF (caudal BF-1 and BF-2, 2 mm and 4 mm to the BF site, respectively) and the amygdala (see Materials and Methods). Although a significant aggravation was observed in the caudal BF-1 site, no significant effect was observed after caudal BF-2 or amygdala injection. Four or five (out of six) narcoleptic dogs were used in each drug session. Each bar indicates the mean baseline level of cataplexy for the overall session (n = 44, 32.9 ± 2.6 sec, mean ± SEM). An asterisk indicates the statistical significance of the change (time course effect) in time spent in cataplexy by the treatment (**p < 0.01, *p < 0.05, a repeated measures ANOVA). 

Carbachol (10 nmol) in the BF significantly increased wakefulness in these animals. This result is consistent with data previously reported in cats using similar doses of carbachol (2.7 nmol bilateral or 22 nmol unilateral) and cataplexy in the mPRF (Valazquez-Mozezuma et al., 1989; Reid et al., 1994a). The finding that physostigmine, a cholinesterase inhibitor, significantly reduced cataplexy, while a selective M1 agonist, McN-A-343, did not aggravate cataplexy (Fig. 3). The effect of carbachol on cataplexy in the BF is, thus, probably mediated by an M2 receptor subtype as it is reported for REM sleep and cataplexy in the mPRF (Valazquez-Mozezuma et al., 1989; Reid et al., 1994a). The finding that physostigmine, a cholinesterase inhibitor, also aggravates cataplexy (Fig. 3) suggests that increases in endogenous ACh levels in the BF could be involved in physiologically triggered cataplexy in narcoleptic dogs.

The same dose of carbachol (10 nmol) did not induce any cataplexy-like muscle atonia in controls. Polygraphic recordings demonstrated that a 10 nmol carbachol injection in the BF significantly increased wakefulness in these animals. This result is consistent with data previously reported in cats using similar doses of carbachol (2.7 nmol bilateral or 22 nmol unilateral) injected into the BF (Sakai et al., 1990; Baghdoyan et al., 1993). Baghdoyan et al. (Baghdoyan et al., 1993) further reported that carbachol injection in the BF of normal cats significantly reduced REM sleep and blocked the ability of REM induction by carbachol injected into the mPRF. Under our recording conditions, however, control dogs had only a small amount of REM sleep at the baseline (1.77% of 4 hr recording time), and no significant decrease (1.56%) was observed after the carbachol injection.
Figure 4. Injection sites of carbachol in the BF a, b. The injection site in the BF and adjacent cholinergic cell groups from one of the narcoleptic dogs is shown. The injection site was revealed (diffuse black area) by an immunohistochemical staining of CTb (injection of 0.1 μl of CTb). Cholinergic neurons, ChAT positive, are observed (small dark brown spots) near the injection site. The injection sites for four narcoleptic dogs (hatched areas) and one control dog (encircled with broken line) in the magnocellular POA at the same AP level (AP 25.0, L 2.0–6.0, H 7.0–13.0 by Lim et al., 1960) are illustrated in one figure. The distribution of ChAT-positive neurons (black dots) from one narcoleptic dog is plotted for reference. Injection sites for two other control dogs were also located in the magnocellular POA at different AP levels (AP 24.5, L 3.0–4.0, H 7.0, and AP 24.0, L 4.0, H 7.0). Injection sites for two other narcoleptic dogs were located in the vertical (AP 28.0, L 2.0, H 7.0) and the horizontal (AP 26. L 6.0, H 7.0) limbs of the diagonal band of Broca. Actual injection sites for the BF were found to vary at most 1–5 mm from the coordinates given in the atlas (Lim et al., 1990), with the observed shift being caudal in most cases. AC, anterior commissure; cd, caudate nucleus; F, fornix; GP, globus pallidus; IC, internal capsule; Pt, putamen; V3, third ventricle.

In this study, we further increased the dose of carbachol up to 50 nmol (unilateral and bilateral) in control dogs and found that 50 nmol of carbachol injected bilaterally induced a cataplexy-like state (sudden onset of complete muscle atonia from active-wake state, see Fig. 6) in all three control animals tested. These results parallel the data of an earlier study by Hernández-Peón et al. (Hernández-Peón et al., 1963), which reported that ACh or carbachol injection into the BF induced desynchronized sleep in normal cats. In that study, the dose of carbachol used was not specified, but was likely to be very large since carbachol crystals were inserted through the injection cannulae. Taken together with results obtained by us and others (Sakai et al., 1990; Baghdoyan et al., 1993) using the lower doses of carbachol, it is suggested that very high doses of carbachol are needed to
trigger REM sleep atonia in normal animals when injected in the BF. The fact that cataplexy can be induced by injecting low doses of carbachol in narcoleptic but not control dogs suggests that affected animals are more sensitive to cholinergic stimulation in the BF. We have previously demonstrated that narcoleptic dogs are hypersensitive to cholinergic stimulation in the mPRE. Therefore, these results suggest that a widespread hypersensitivity to cholinergic stimulation might underlie the pathophysiology of canine narcolepsy.

In both the pons and the BF, cholinergic stimulation in the vicinity of cholinergic neurons elicits REM sleep and/or cataplexy. In the pons, the most sensitive area does not overlap with the LDT-PPT areas (see Jones and Beaudet, 1987; Vincent and Reiner, 1987; Mitani et al., 1988; Shiromani et al., 1988). This suggests that the effects of carbachol are mediated via the stimulation of noncholinergic, but cholinoceptive neurons. Lydic et al. (1991) recently demonstrated that unilateral administration of carbachol into the mPRF of cats triggers a REM sleep-like state with an increase of ACh in the contralateral mPRF, where the main source of cholinergic input is from the MPT (Mitani et al., 1988; Shiromani et al., 1988). This suggests that the stimulation of cholinoceptive mPRF neurons by carbachol secondarily activates MPT cholinergic neurons. In our study of the BF, the carbachol-sensitive area corresponds closely to the magnocellular BF cholinergic neurons (Fig. 4). It was not possible to distinguish cholinergic and cholinoceptive areas because cholinergic neurons are more dispersed and intermingled with noncholinergic neurons in the BF than in the pons (Martines-Murillo et al., 1990; Fort et al., 1992). Thus, both cholinergic and cholinoceptive neurons could be involved in the cataplexy-inducing effects of carbachol injections in the BF. A recent electrophysiological study on guinea pig brain slices demonstrated that an application of muscarine hyperpolarizes cholinergic neurons in the BF (Khatib et al., 1991). In contrast, an in vivo study has shown that putative BF cholinergic neurons antidromically driven from the neocortex are excited by iontophoretic

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Figure 5. Effect of the BF carbachol injections on specific sleep stages in narcoleptic and control dogs. Carbachol (10 nmol) was injected unilaterally into the BF of five narcoleptic (one session for each animal) and three control (two sessions for each control animal) dogs for polygraphic recordings. Carbachol injections induced long-lasting muscle atonia (without REMs, see Materials and Methods) in narcoleptic dogs for as much as 30% of the 4 hr recording period. SWS was significantly reduced. In control dogs, the same dose of carbachol (10 nmol) did not induce any cataplexy-like behavior, while it significantly increased the time spent in wakefulness and significantly reduced SWS. Asterisks indicate significant changes (***p < 0.01, *p < 0.05, paired samples t test) from the saline session.

Figure 6. Cataplexy-like behavior can be induced in control animals after injecting high dose of carbachol (50 nmol, bilaterally) into the BF. Unilateral injections (10-50 nmol) did not induce cataplexy in control dogs (n = 3, one session for each dose), while a very high dose of bilaterally injected carbachol (50 nmol) induced a sudden onset of muscle atonia with desynchronized EEG in all control dogs tested (one session for each of three dogs tested). The effect occurred 10-20 min after injection and lasted up to 2 hr. The polygraphic result of a typical experiment obtained in a control dog is shown.
administration of carbachol or muscarine in the BF (Lamour et al., 1986). This may suggest that the carbachol injection in the BF stimulates noncholinergic cells, which then secondarily stimulates cholinergic neurons, as has been suggested in the mesopontine neurons (see Lydic et al., 1991). This could result in a global activation of a whole network of cholinergic cells that might mediate REM sleep-like state changes. The fact that many cholinergic cells in both the BF and MPT have similar electrophysiological properties in vitro (Kamondi et al., 1992; Khateb et al., 1992) further supports the possibility of similar cholinergic-cholinoceptive interactions in both brain areas.

It still remains to be established how pontine and BF cholinergic systems are coordinated during normal and dissociated REM sleep events. In the pons, the region sensitive to cholinergic stimulation is large, and individual behavioral features of REM sleep, such as atonia or ponto-geniculo-occipital waves, can be produced, depending on the stimulation of the specific subregions and the dose of carbachol used (George et al., 1964; Miller and Dement, 1974; Valazquez-Mozejuma et al., 1989; Baghdoyan et al., 1984; Hobson et al., 1993). Similarly, cholinergic stimulation with small doses of carbachol (5 nmol unilateral), as far from the pons as the caudal medulla, can also elicit atonia in cats (Lai and Siegel, 1988). In our study, a very high dose of carbachol injected in the BF of control dogs elicited atonia. The BF region may, therefore, represent the most rostral part of an extended cholinoceptive system, as suggested by Hernández-Peón et al. (1963). We hypothesize further that cholinergic cell groups in the brainstem and the BF are coordinated via their interactions with cholinoceptive neurons. This cholinoceptive system may be involved in ensuring that a global activation of all REM-on cholinergic neurons is maintained in normal conditions once the transition into REM sleep occurs.

That emotional excitation triggers cataplexy is one of the hallmarks of narcolepsy. The BF is anatomically connected with the limbic system, which is believed to be involved in the control of emotions (see Papez, 1937). Furthermore, BF neurons are known to respond to the arousing quality of appetitive stimuli (Rolls et al., 1979; Richardson and Delang, 1991), which is the stimuli we use to induce cataplexy in narcoleptic dogs. For this reason, cholinergic mechanisms within the BF rather than in the mPFC are more likely to be the initiators of cataplexy. We hypothesize that emotional excitation increases ACh release in the BF. Accordingly, in control animals, this would produce alertness in the same way after the injection of low doses of carbachol (Fig. 5). In narcoleptic dogs, however, the same increase in ACh release during emotions could stimulate a population of hypersensitive cholinoceptive cells. This stimulation would then activate cholinergic cells in the brainstem, resulting in cataplexy or other dissociated REM sleep events. This theoretical model would also explain why very extreme emotional circumstances, such as intense laughter, have been reported to induce muscle weakness in some normal individuals (Guilleminault et al., 1974). This phenomenon could be explained by an extremely high acetylcholine release in the BF that would be sufficient to overstimulate the system in the absence of any underlying hypersensitivity.

Human studies have demonstrated that symptomatic narcolepsy occurs more frequently in association with lesions of the diencephalon (hypothalamus and third ventricle) than with lesions of the midbrain or pons (Aldrich and Naylor, 1989; Onofrj et al., 1992), suggesting the involvement of forebrain structures in narcolepsy. In this study, we have demonstrated that a cholinoceptive site in the BF is hypersensitive in canine narcolepsy. This hypersensitivity might be primary or secondary to an abnormality in other neurotransmitter systems. Our series of neuropharmacological and neurochemical studies on canine narcolepsy have suggested that a hyperactivity of monoaminergic systems is implicated in the pathophysiology of canine narcolepsy (see Nishino et al., 1994, for review). It is well known that the activity of adrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe is abolished during REM sleep (McGinty and Harper, 1976; Aston-Jones and Bloom, 1981). The monoaminergic activity is known to influence the responsiveness of REM sleep/wakefulness state changes to cholinergic stimulation: for example, administered physostigmine enhances arousal during wakefulness (Yamamoto and Domino, 1967), while it induces REM sleep when administered in reserpine-induced monoamine depletion conditions (Karczmarski et al., 1969). Therefore, an abnormally reduced monoaminergic tone could also be a causative factor in canine narcolepsy. Cholinergic hypersensitivity, however, is likely to be the critical step leading to the abnormal REM sleep phenomena of narcoleptic dogs.

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