Sleep Suppression after Basal Forebrain Lesions in the Cat

Abstract. *Large bilateral preoptic lesions produced complete sleeplessness in two cats. In eight additional cats, similar but smaller lesions resulted in a significant reduction of quiet (slow-wave) sleep by 55 to 73 percent, and active (paradoxical) sleep by 80 to 100 percent. These values were determined by pre- and postlesion 22-hour continuous observations. Complete sleeplessness was followed by lethal exhaustion within a few days, whereas incomplete sleeplessness persisted at maximum levels for 2 to 3 weeks. The suppression of sleep was characterized by a gradual onset during the first 1 to 2 weeks, and a complete or partial recovery after 6 to 8 weeks. The severity of sleep suppression was found to be related to the size and localization of lesions placed specifically within the preoptic area and not to transient disturbances in feeding and temperature regulation.*

Two distinct types of sleep, quiet sleep and active sleep (*1*), recur in a stable pattern in many adult mammals (*2, 3*). Investigations of the neural mechanisms regulating these behavioral states have focused on sleep-inducing structures localized in the caudal brain stem (*4*). There is evidence, however, that the forebrain also contains mechanisms which can initiate sleep. After complete transection of the midbrain, the forebrain at first shows continuously synchronized electroencephalographic (EEG) potentials, suggestive of quiet sleep, and later, provided that the animal is carefully maintained, shows regular alternating periods of desynchronized electrocortical potentials, suggestive of wakefulness or active sleep, and synchronized electrocortical potentials (*5*).

Electrical or chemical stimulation of several forebrain sites, including the basal forebrain, thalamus, and frontal cortex, have been found to produce sleep in waking cats (*6, 7*). However, studies of the effects of experimental lesions of these forebrain sites have not provided definitive evidence for sleep-inducing mechanisms (*8*). The most striking report is that of Nauta (*9*) who observed that transections of the anterior hypothalamus at the level of the optic chiasm in the rat resulted in continuous motor hyperactivity and subsequent death within a few days. These observations were made, however, without the advantages of electrographic recording techniques and before the discovery of a distinction between quiet sleep and active sleep.

The present study confirmed with cats Nauta's experiment with rats, and in addition (i) examined both electrographic and behavioral correlates of sleeplessness, (ii) employed discrete electrolytic lesions in an attempt to localize the sleep-inducing system, (iii) investigated the relative effect of lesions on quiet sleep and active sleep, and (iv) quantified the lesion effects with long-term observations.

Sleep and waking patterns were assessed in 18 adult cats in continuous 22-hour recordings of EEG, eye movement, and neck electromyographic (EMG) activity, by using chronically implanted electrodes (*3*). Recording sessions were completed both before placement of forebrain lesions and on six predetermined dates afterward (3 days, 1, 2, 3, 4, 6 to 8 weeks). The 22-hour records were classified into four states, wakefulness, drowsiness, quiet sleep, and active sleep, according to criteria described previously (*3*). Experiments were accomplished in soundproof chambers where recordings were obtained through a flexible cable and slip-ring system connected to a Grass polygraph. Food was available at all times, and when lesions depressed spontaneous feeding, animals were maintained by forced feeding. Chamber temperature was maintained at 23° ± 2°C, and lighting was automatically controlled on a 12-hour-bright and 12-hour-dim cycle. Lesions were produced at the base of the forebrain in the region dorsal to the optic chiasm by passing an anodal d-c current of 2 to 5 ma for 20 to 60 seconds, through each of four to eight electrodes. The uninsulated electrode tips were oriented in a row perpendicular to the midline plane. These electrodes were chronically implanted to allow a comparison of prelesion and postlesion recordings without the complication of intervening anesthesia and surgery. The neck electrodes served as the cathode.

In ten cats lesions produced a significant and prolonged reduction in sleep, while in eight others the lesions were ineffective or produced short-lasting (3 to 7 days) effects. Histological analysis showed that all effective lesions were localized in the preoptic–basal forebrain area over the optic chiasm. Among the damaged structures were the medial forebrain bundle, the supraoptic nucleus, the lateral preoptic nuclei, and the inferior thalamic peduncle. The eight lesion sites which yielded no effects, or minimum short-lasting effects, included the optic chiasm and adjacent suprachiasmatic nucleus, the rostral path of the medial forebrain bundle (with extensive damage to adjacent meningeal layers), and the neighboring dorsal structures (including the bed nucleus of the stria terminalis, and the fornix, with enlargement of the lateral ventricles). Extensive unilateral preoptic damage, or lesions destroying less than 30 percent of a cross section of the preoptic area, were also ineffective. Large symmetric lesions were required to produce sleeplessness, suggesting that sleep is facilitated by a relatively diffuse neural system.

Table 1 shows the deficits in both quiet sleep and active sleep resulting from the ten effective lesions. In two of the cats sleep was completely suppressed on the 7th day after the lesions. These animals died within 10 days, but continuous observations on the 7th day revealed that they were constantly standing or walking in the chamber.

Table 1. Percentage depression of quiet sleep and active sleep after preoptic–basal forebrain lesions. The numbers in each pair refer to quiet sleep and active sleep, respectively, and were based on comparison of sleep patterns in individual 22-hour recording sessions from before and after lesions in each cat. Sleep was totally abolished in two cats. The depression of sleep is evident 3 days after the lesions but maximum depression occurs after 1 to 3 weeks. After 4 to 8 weeks some recovery from the maximum deficits was observed.

Cat	Percentage change: quiet sleep; active sleep		
	3 days after lesions	Maximum depression	4 to 8 weeks after lesions
1	−28; −40	− 67; − 90	+13; 0
2	−12; −83	− 73; −100	−32; −25
3	− 8; −50	− 68; − 86	+6; −7
4	−14; −89	− 65; −100	−11; −56
5	−62; −88	− 62; − 94	−40; −59
6	−64; −92	− 67; −100	− 8; −15
7	−60; −79	− 64; − 84	Dead
8	−48; −79	−100; −100	Dead
9	−33; −64	− 55; − 86	−14; −36
10	−31; −83	−100; −100	Dead
Means*	−36; −75	−72; − 94	−12; −28

* The differences between the means for columns 2 and 4, 4 and 6, 3 and 5, and 5 and 7 are significant by the *t*-test ($P < .01$).

Subsequently, they appeared to become exhausted and lay with their limbs splayed. If they were lifted to their feet and released, they immediately collapsed. However, EEG and EMG patterns continued to indicate wakefulness. In each of the eight additional cats, lesions were followed by an incomplete suppression of quiet sleep and active sleep, but the reduction in both states was statistically significant (t-tests, $P < .005$) during each of five recording dates in the first 4 weeks after the lesions. An example is shown in Fig. 1. The percentage depression of active sleep was always greater than the depression of quiet sleep. Active sleep was always reduced to less than 20 percent of the normal amount, and in three of the eight cats this state was completely eliminated during at least one recording session. Active sleep was eliminated in every case when the amount of quiet sleep was reduced to 15 percent ± 5 percent, of recording time. When the amount of quiet sleep exceeded this minimum level the amount of active sleep was approximately one-third of the additional quiet sleep.

As shown in Table 1, a depression in sleep was observed by day 3 following the placement of lesions, but maximum effects, including the cases of complete insomnia, appeared after 1 to 3 weeks. The depression persisted at the maximum levels for 2 to 3 weeks. However, by 4 to 8 weeks after the lesion significantly increased amounts of both sleep states were observed in each cat, indicating partial recovery from the lesion. In two cats recovery appeared to be complete after 6 weeks. The depression of sleep was reflected as an increase in wakefulness rather than drowsiness. Drowsiness was abolished in the two cats which were completely sleepless. In other cats there were some fluctuations in the amount of drowsiness, but these were not consistent.

Waking behavior prior to recovery was characterized by very long periods of quiet sitting, standing, and walking within the recording chamber, but postural mechanisms appeared to be normal. Responsiveness to all modes of sensory stimulation, however, was markedly depressed.

The lesions were followed by deficits in feeding and temperature regulation in addition to those in sleep. Aphagia and adipsia lasted for a period of 1 to 3 weeks; however, spontaneous feeding of palatable food reappeared while the effects of the lesions on sleep patterns were still marked. Disturbances in temperature regulation were variable, but frequently consisted of an initial hypothermia, a 1° to 3°C temperature drop lasting for 1 to 5 hours after lesions, and a subsequent hyperthermia, a 1° to 2°C elevation lasting 1 to 5 days. Rectal temperature then returned to the normal range.

These data show that the preoptic–basal forebrain area contains neural structures whose integrity is essential for the normal pattern of sleep and wakefulness. Increased wakefulness, which constituted the most prolonged consequence of these lesions, may reflect the fact that the brainstem reticular arousal system was released from antagonism by basal forebrain structures. The antagonism of reticular arousal systems by basal forebrain activation has been documented in behavioral studies (*10*), but the underlying mechanisms are not known.

Both quiet sleep and active sleep are thus apparently dependent upon structures within the preoptic–basal forebrain region. Since complete midbrain or rostral pontine transections do not prevent the occurrence of electrographic and behavioral signs of active sleep below the transection (*11*), it is surprising that a discrete lesion in the forebrain can suppress these signs. These lesions must release a process which inhibits the brainstem mechanisms of active sleep. The existence of a forebrain mechanism that can inhibit active sleep is supported by observations of the changes in sleep patterns that have been recorded during ontogeny. Infant mammals exhibit a very high proportion of active sleep which is, however, gradually reduced to adult levels during postnatal maturation (*12*). This type of developmental change can result from the maturation of forebrain neural systems that suppress primitive mechanisms organized in lower structures (*13*).

These conclusions are based on the assumption that the destruction of preoptic structures, and not lesion-induced irritation of adjacent tissues, was re-

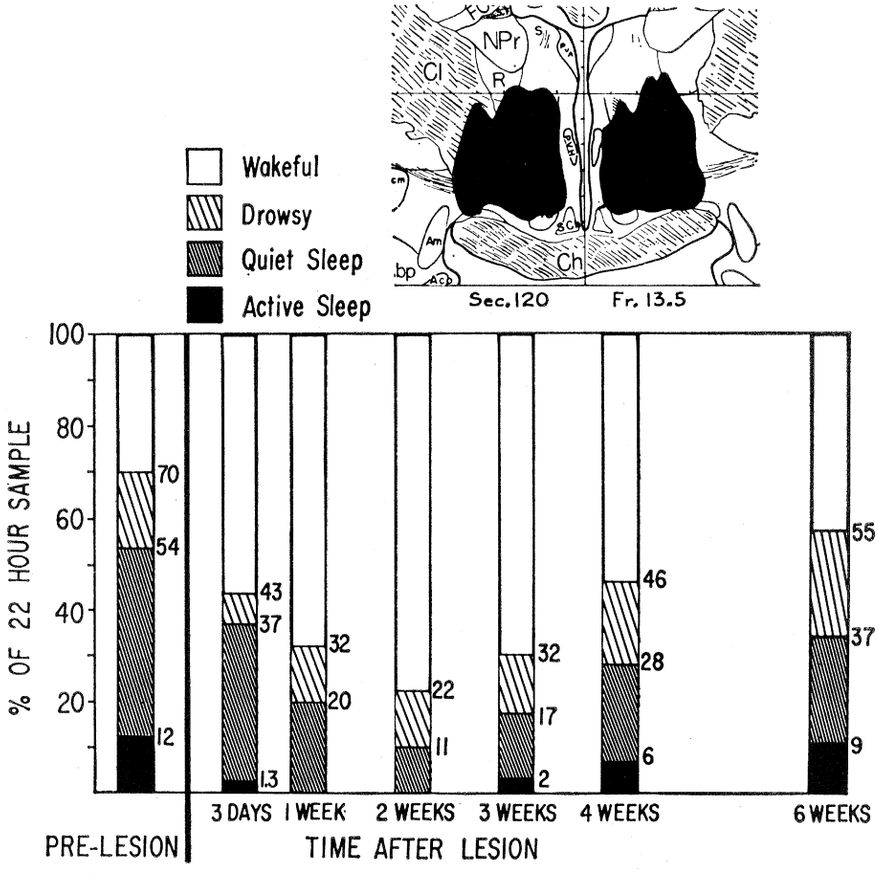

Fig. 1. The effects of preoptic–basal forebrain lesions on the percentages of sleep and waking patterns in 22-hour recordings from cat No. 2. Sleeplessness developed gradually, reaching a peak after 2 weeks, and showed a progressive recovery thereafter. (Numbers beside the bars indicate cumulative percentages.)

sponsible for our findings. This assumption is consistent with the reports that both electrical (*7*) and chemical (*14*) stimulation of this region can induce sleep. Moreover, it is also supported by the observation that symmetric bilateral lesions were required to produce sleeplessness, while unilateral irritative stimulation should be sufficient to produce arousal. Irritative effects of electrolytic lesions in the preoptic area have been implicated in several behavioral and physiological disturbances (*15*), but these phenomena were observed during the first 24 hours after the lesions, whereas hyposomnia showed a gradual onset. The postlesion hypothermia in the present study may also reflect a transient irritative phase. The lesion-induced disturbances in feeding and temperature regulation would be expected on the basis of the known hypothalamic involvement in these functions.

The gradual development of sleeplessness has a time course similar to the onset of supersensitivity to electric shock in rats after posterior hypothalamic lesions (*16*). Other gradual lesion deficits may frequently go unnoticed because investigators often delay testing for at least a week after surgery. The recovery from partial sleeplessness is similar to the recovery from other behavioral deficits after discrete lesions at all levels of the neuroaxis (*17*). The phenomenon of recovery suggests that these lesions depress, weaken, or disrupt, rather than destroy, the sleep-inducing mechanism. The observation of death after preoptic lesions agrees with the report of Nauta in the rat (*9*). In the cat, death occurred about 10 days after the lesions (*18*), and was related to the degree of sleeplessness, although other lesion-induced dysfunctions may have been contributing factors. A critical physiological need for sleep is also indicated by reports of death following prolonged experimental deprivation of sleep (*19*), but the basis of this need remains unknown.

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References and Notes

1. Quiet sleep is synonymous with "slow-wave spindle-burst sleep," or "synchronized sleep." Active sleep is synonymous with "paradoxical sleep," or "rapid eye-movement (REM) sleep." The terms "quiet sleep" and "active sleep" refer to the amount of visible motor activity and were selected because they imply no specific underlying neural mechanisms and do not depend on any single criterion.
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20. This research was supported by the Veterans Administration, and NIH grant MH-10083.

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Visible Light: Mutagen or Killer?

The evidence that intense visible light produces permanently "bleached" (that is, aplastidic) colonies in euglena is fascinating (*1*). However, I disagree with Leff and Krinsky's interpretation that visible light acted as a mutagen. The observations they present do not contradict Zelle and Hollaenders' generalization that "light with wave lengths above 300 nm has primarily lethal action but very little mutagenic action" (*2*). Their data in fact show that visible light in the presence of oxygen acts as a lethal agent, not a mutagen.

Killing is easier than mutating; a list of lethal agents will always be longer than a list of mutagens. It seems to me that most of the work on euglena (*3*) supports the concept that permanent "bleaching agents" are chemicals and treatments which eliminate the genetic potential of euglena cells to form chloroplasts. The chloroplast has been envisioned as a once free-living photosynthetic symbiont, presumably homologous to blue-green algae (*4*). The most logical interpretation of the data is that the "bleaching agents" for example, light and oxygen (*1*); *O*-methylthreonine, benadryl, streptomycin, heat, and ultraviolet treatments (*3*); and nitrosoguanidine (*5*) are not mutagens; they are simply chemicals and treatments more lethal to the plastid symbionts than to the host cells (*6*). This interpretation is consistent with the failure to find "back mutation" in the euglena plastid "bleaching" system and with the so-called anomalous "100 percent mutation rate" (*7*).

The dangerous effects of intense visible light in the presence of gaseous oxygen seem to be more complicated than those of other "bleaching agents"; they threaten the lives of both the symbiotic plastid and the host cell. Unlike streptomycin and ultraviolet light, light and O_2 do not demonstrate the clear-cut differential sensitivity of the plastid system (that is, loss of the plastid system in the absence of cell death). Table 1 of Leff and Krinsky's data shows that the plastid system is just slightly more sensitive to light than the rest of the cell is. For example, only about 0.1 percent of the euglena cells exposed to 5 hours of light intensities comparable to bright sunlight survive at all, and for the most part (about 93 percent of the time) these survivors retain their plastids.

Just as the DNA isolated from the