A RE-EVALUATION OF THE EFFECTS OF LESIONS OF THE PONTINE TEGMENTUM AND LOCUS COERULEUS ON PHENOMENA OF PARADOXICAL SLEEP IN THE CAT

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Abstract. Bilateral lesions placed in the pontine tegmentum resulted in episodes of paradoxical sleep in which the characteristic atonia of that sleep stage was absent in six cats. Following each period of synchronized sleep, in which the degree of muscle tone of the dorsal cervical muscles gradually diminished, cats with such lesions would slowly raise their heads, move their limbs at all joints, make several attempts to rise and eventually leap violently. During such episodes they were unresponsive to strong lights, touching and mild pinching. Only sound would arouse them. This behavior appeared as early as the 2nd postoperative day, the 1st day of recording. Such episodes supplanted normal paradoxical sleep with atonia and lasted unchanged for as long as 6 months in one cat until it was killed while still in good health. Complete recovery of atonia was observed in one cat after 3 weeks. Either no recovery or else eventual recovery to excessively active periods of paradoxical sleep while remaining recumbent characterized the sleep of the other four. The conclusion drawn from these experiments and from a review of the literature is that the hypotheses stating that the locus coeruleus or other isolated nuclei of the pons are specifically concerned with the initiation of paradoxical sleep are not clearly supported by available evidence.

INTRODUCTION

The discovery of paradoxical sleep (1, 4, 11), in which the electroencephalogram exhibits a pattern resembling that of wakefulness while the body musculature is tonically paralysed due to the inhibition of α-motoneurons (7, 20), has led to the efforts of many investigators to determine the structure responsible for this stage of sleep. To answer this question ablations of various portions of the central nervous system have been made in order to determine whether or not paradoxical sleep
would occur in the absence of the areas removed. Such experiments have led to the belief that the rostral pons is a site which is critical for the appearance of paradoxical sleep. Brain-stem transections above this level do not prevent peripheral manifestations of paradoxical sleep, such as periodic muscle atonia, and even the rapid eye movements associated with this sleep state, if the cut is rostral enough (9, 10, 27). More caudally placed transections prevent the occurrence of any of the phenomena associated with paradoxical sleep (10). The result of somewhat smaller lesions within the rostral pons led Jouvet (10) and Carli and Zanchetti (3) to designate the region of the nucleus reticularis pontis caudalis or the nucleus reticularis pontis oralis as the neuronal aggregates responsible for triggering the appearance of paradoxical sleep in the cat. According to these authors, bilateral lesions involving these nuclei suppressed or abolished the appearance of paradoxical sleep.

Later, Jouvet (12) emphasized that the locus coeruleus, densely populated by noradrenergic neurons in the dorsolateral pontine tegmentum, was the triggering zone for paradoxical sleep. His reasons for designating a new site were based on certain extrapolations from pharmacological experiments and the fact that lesions of the locus coeruleus suppressed paradoxical sleep for as long as 2 or 3 weeks (14, 25). When paradoxical sleep reappeared, the typical atonia was not present. Instead, after a period of synchronized sleep cats would raise their heads and appear to be hallucinating. The cats had miotic pupils and relaxed nictitating membranes although they exhibited signs of rage and sexual behavior. The cats were unresponsive to external stimuli during this state. There was generally fast cortical activity and the EMG activity of the neck was increased. Episodes of such behavior always followed periods of synchronized sleep, as does paradoxical sleep, and comprised about the same percentage of total sleep time. It was suggested, therefore, that this hallucinatory-like behavior represented paradoxical sleep without atonia. Similar behavioral observations were not reported by Carli and Zanchetti (3), who involved the locus coeruleus in some of their experiments.

The present investigation has confirmed the fact that bilateral lesions placed within the pontine tegmentum result in periodic episodes resembling hallucinatory behavior and has added the observation that such episodes can permanently supplant normal paradoxical sleep. Furthermore, we argue that abolition of the atonia of paradoxical sleep is the main effect of such lesions and that complete, selective abolition of the triggering of paradoxical sleep by means of pontine lesions has not yet been convincingly demonstrated. The results and conclusions of this study have already appeared in preliminary form (8).
MATERIAL AND METHODS

Electrolytic lesions were placed bilaterally in the pons in seven cats by introducing the electrode through the cerebellum 45° from the horizontal plane and parallel to the sagittal plane. To control for the effect of cerebellar damage by the electrode penetrations, two animals (KH6 and KH13) were independently lesioned in the cerebellum (see Table I).

Attempts to place pontine lesions by ventral surgical approaches resulted in the deaths of four additional cats.

Under sterile conditions stainless steel screw electrodes were implanted for electroencephalographic (EEG) and electro-oculographic recordings (EOG). Stainless steel wires sutured into the dorsal cervical muscles served as electromyographic (EMG) electrodes.

Recordings were usually performed for a 4 to 5-hr period in the middle of the day, although 24-hr recording was used in one cat (KH1). They were conducted under well-lit conditions to permit simultaneous behavioral observations. The cats were kept in transparent plastic cages during the recording sessions. KH12 and KH13 were further separated from the experimenter by a one-way mirror. At first, the recording instrument was a Grass model 111D EEG machine. Later, a Beckman Type R Dynograph recorder was used. Important behavior was filmed or videotaped.

All cats were subjected to thorough neurological examinations, pre- and postoperatively. The cats were studied for as long as 6 months postoperatively. All were maintained in excellent physical condition throughout the experimental period. Then they were anesthetized with pentobarbital sodium and perfused intracardially with warm physiological saline and 10% formalin solutions. Brain blocks were embedded in celloidin. Histological sections were cut at 30 μm and stained alternately with cresyl violet and Mahon’s stain in order to determine the lesion sites.

RESULTS

Lesions

Lesions made within the pons are illustrated in Fig. 1–3. Figure 3 consists of photomicrographs of the sections used to illustrate KH6’s lesion in Fig. 1. Lesions which were effective in eliminating atonia in paradoxical sleep partially damaged the locus coeruleus and nucleus reticularis pontis oralis. In the cases illustrated in Fig. 2 the lesions
Fig. 1. Cross-sections through the brain stem of four cats with pontine lesions (black). Stereotaxic levels P1 to P4 are shown from left to right. KH3 never exhibited paradoxical sleep without atonia. The phenomenon occurred in the others. All others eventually showed some recovery. Abbreviations for this and subsequent Figures: BC, brachium conjunctivum; IC, inferior colliculus; LC, locus coeruleus; RF, reticular formation; RPO, nucleus reticularis pontis oralis.
extended as far caudally as the motor nucleus of the trigeminal nerve (not illustrated). The most long-lasting effects were observed in the cases illustrated in Fig. 2. KH3 (Fig. 1) was the only animal with pontine lesions which had no observable alteration of motor control during paradoxical sleep.

Damage to the fastigial nuclei of the cerebellum alone in KH6 and KH13 (see Table I) produced no alteration of paradoxical sleep atonia although there were effects observed in synchronized sleep (see below) which form the basis of another report (19). Retrograde cerebellar damage, primarily of the fastigial nuclei, was also seen in all cats except KH1 (see Table I).
### TABLE I
Summary of pontine lesion effects

<table>
<thead>
<tr>
<th>Cat</th>
<th>Pontine lesions</th>
<th>Fastigal lesions</th>
<th>Abolition of atonia</th>
<th>Rage</th>
<th>Duration of episodes</th>
<th>Frequency</th>
<th>Recovery of atonia</th>
<th>Post-operative survival time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KH1</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>decreased&lt;sup&gt;c&lt;/sup&gt;</td>
<td>increased</td>
<td>partial</td>
<td>2</td>
</tr>
<tr>
<td>KH2</td>
<td>yes</td>
<td>yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>yes</td>
<td>no</td>
<td>decreased&lt;sup&gt;c&lt;/sup&gt;</td>
<td>increased</td>
<td>no&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2</td>
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<tr>
<td>KH3</td>
<td>yes</td>
<td>only unilateral</td>
<td>no</td>
<td>no</td>
<td>normal</td>
<td>normal</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>KH4</td>
<td>yes</td>
<td>yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>yes</td>
<td>some rage</td>
<td>decreased&lt;sup&gt;c&lt;/sup&gt;</td>
<td>increased</td>
<td>no</td>
<td>6</td>
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<tr>
<td>KH5</td>
<td>yes</td>
<td>yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>partial</td>
<td>no</td>
<td>decreased&lt;sup&gt;c&lt;/sup&gt;</td>
<td>increased</td>
<td>full&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>KH6</td>
<td>yes</td>
<td>yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>yes</td>
<td>rage</td>
<td>decreased</td>
<td>reduced</td>
<td>partial&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5</td>
</tr>
<tr>
<td>KH12</td>
<td>yes</td>
<td>yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>yes</td>
<td>rage in most episodes</td>
<td>decreased</td>
<td>increased</td>
<td>no</td>
<td>4</td>
</tr>
<tr>
<td>KH13</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>normal</td>
<td>normal</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>a</sup>, primarily severe retrograde degeneration. Moderate degeneration was also seen in the interpositus nuclei; <sup>b</sup>, 1 month prior to pontine lesion; <sup>c</sup>, episodes could last as long as 8-10 min; <sup>d</sup>, no signs of recovery when killed 2 months postoperatively; <sup>e</sup>, after 3 weeks; <sup>f</sup>, after 3 months.
Fig. 3. Photomicrographs of the sections of KH6 from which Fig. 1 was made. Arrows point to the lesion. Abbreviations as in Fig. 1.
Fig. 5. KH4 at the initiation (left) of an episode of paradoxical sleep without atonia and fully erect (right) during the same episode. Note the relaxed nictitating membranes. Frames from a movie taken with floodlamps 1 month after lesioning.

Fig. 6. KH4 during (left) and just after spontaneous arousal (right) from paradoxical sleep without atonia. Note the relaxed and retracted nictitating membranes respectively. Frames from a movie taken with floodlamps 1 month after lesioning.
Behavior during sleep following pontine lesions

KH3 showed normal paradoxical sleep postoperatively. The other six cats exhibited abnormal behavior during what we believe to be paradoxical sleep as early as 2 days (KH1) after the pontine lesioning. During such episodes the characteristic atonia of paradoxical sleep was lacking (Fig. 4). Each episode followed a period of synchronized sleep in which the tone of the dorsal cervical muscles had gradually diminished. The episodes of synchronized sleep usually lasted approximately 20 min.

The episodes began with elevation of the head and isolated movements of the limbs, such as flexion-supination of a forelimb, or stepping movements of the hindlimbs (Fig. 5A). After the animal had righted itself, the head often moved forward and sideways in an ataxic, searching manner. Included in each episode were several attempts at standing (Fig. 5B), interrupted by periods in which the head and shoulders were lowered and the cat was quiescent. The violence of the movements increased in all cats as the episode progressed although the intensity of activity waxed and waned throughout. Paradoxical sleep almost always terminated as the cats convulsed while recumbent or actually stood and leaped forward or backwards.

Fig. 4. Continuous record of the electroencephalogram (EEG), electromyographic activity of the dorsal cervical muscles (EMG), and the electro-oculogram (EOG). The record in A is from an episode of synchronized sleep. Note the transition in B from high-amplitude to low-amplitude EEG activity and the gradual increase in the EMG in C, signalling the beginning of an episode of paradoxical sleep without atonia.
During these periods, the eyes were always open, the pupils fissurated, and nictitating membranes relaxed (Fig. 6A). The cats did not respond to the sudden onset of intense light produced by 300-w photoflood lamps, which were used while recording the behavior on film. Tactile stimulation or moderate tail pinch failed to arouse them. However, sounds, such as those made by the creaking of an experimenter’s bending knee, woke them rather easily. When the cats were aroused, their nictitating membranes retracted immediately (Fig. 6B), and they oriented to visual stimuli.

Short-lasting signs of rage or fear, such as facial grimaces, dilation of the pupils, retraction of the nictitating membranes, piloerection and arching of the back were seen in KH6 and KH12, and on rare instances in KH4. KH12 developed over time violent, convulsive episodes with frequent displays of rage, followed by wild searching and tail-biting at the time of arousal. This pattern of behavior, which was characteristic for KH12 only, most nearly resembled that described by Jouvet and Delorme (14); while the less violent pattern of behavior of the other cats paralleled that described in the longer report by Roussel (25).

KH5 exhibited some aspects of the behavior described for the other cats. She raised her head intermittently while swinging it from side to side or moved violently in paradoxical sleep.

As in normal paradoxical sleep, the electroencephalogram during these episodes showed low-voltage, fast activity (Fig. 4). As the cat progressed from synchronized sleep (Fig. 4A) into abnormal paradoxical sleep, i.e., without atonia and with elaborate motor behavior, neck activity associated with head movements accompanied the desynchronization of the electroencephalogram (Fig. 4C). The electro-oculogram indicates some eye movements during paradoxical sleep without atonia (Fig. 4C); however, it is probable that these waves represent movement artefacts. The rapid eye movements so characteristic of normal paradoxical sleep were seen only once when the eyes could be observed directly in between convulsive-like movements in KH6.

Episodes occurred when KH1 was first observed 2 days postoperatively and within 3 or 4 days in the remaining cats with larger lesions. (KH4 was not recorded from for the first 9 postoperative days due to absence of the experimenters, but exhibited the full phenomenon at the first recording session). The postoperative recovery period in the latter cats included prolonged recovery from pentobarbital narcosis and, later, incessent slow extensions of the head while a slow wave pattern was present on the EEG. When the head reached a partially opisthotonic position, a brief arousal would occur, followed by ventroflexion of the neck. During this period the cats seemed unable to keep their heads
on the floor; as a result, if they entered synchronized sleep, they would lie with their heads elevated while resting against the side of the observation cage. (This early behavior resembled that seen in cats with only postbrachial spinal cord transections (18).)

Two observations argue against the notion that paradoxical sleep had been selectively suppressed by destruction of a center for paradoxical sleep: (i) KH1, who was otherwise practically normal in wakefulness (see below), exhibited normal synchronized sleep, demonstrated paradoxical sleep without atonia almost immediately and showed only such episodes in one 24-hr recording session; (ii) the other cats also showed severe alterations in both wakefulness and synchronized sleep as a result of the lesions. They remained somnolent unless stimulated awake for feeding. Also, the initial exaggeration of antigravity tone appeared to prevent their assuming a normal curled sleep posture. In the first few days those with the severest signs of cerebellar damage (KH4, KH6, KH12) frequently lay in an opisthotonic position.

KH1 and KH5 had the same amount of paradoxical sleep after the lesion as before, 8–10% of the recording session. There was a decrease in the percentage of paradoxical sleep in KH2, KH4, KH6 and KH12 postoperatively — 5% of the recording session — which was due to a reduction in the duration of the episodes. Although episodes could last as long as 10 min in these cats, they were often shorter in duration, sometimes lasting no longer than 30 sec if especially violent activity occurred. The frequency of appearance of episodes, though, was greater than normal. In the case of the short, violent episodes, sometimes as many as four or five episodes would occur in a 30-min period. Naturally the synchronized sleep episodes were shorter at these times. Because the experimenter was in the same room as the animals, often manipulating them in order to test their reactivity, and because the violent arousals frequently disturbed the sleeping patterns of these cats, it is not possible to state that the pontine lesions were solely responsible for reduction in the amount of paradoxical sleep during the recording sessions.

KH2, KH4, and KH12 showed no recovery of the atonia of paradoxical sleep throughout their survival periods, which ranged from 2 to 6 months. They were all killed in order to examine the lesion sites. KH1 partially recovered so that after three weeks periods of muscular atonia alternated with only occasional head raises during paradoxical sleep. Rapid eye movements clearly distinguishable from movement artefacts reappeared on the recordings with the return of atonia. For the remainder of her 2-month survival period this cat had excessively active paradoxical sleep with considerable movement of proximal
musculature. KH6 recovered to the same degree that KH1 did within 4 months except that KH6 was extremely restless and would sleep very little at the end of her survival period when the experimenter was in the room. In the third survival month she still exhibited fully developed episodes of paradoxical sleep without atonia. KH5, on the other hand, recovered completely after 3 weeks.

Behavior in synchronized sleep was also altered in all cats except KH1. Extensor or flexor thrusts of the limbs persisted throughout synchronized sleep during the postoperative period. Control cerebellar lesions in KH6 and KH13 revealed that this activity in synchronized sleep could be induced by cerebellar lesions alone (see 19).

In general the severity and longevity of the effects were correlated with the size of the lesion. KH3 with the smallest lesion failed to show any change in paradoxical sleep postoperatively (Fig. 1); while KH4 with the biggest lesion showed the full phenomenon of paradoxical sleep without atonia throughout her 6-month postoperative survival period. KH2 and KH12 (Fig. 2) had large lesions and showed no signs of recovery when sacrificed 2 or 4 months postoperatively. KH1, who recovered from a full phenomenon to a partial one, and KH5, who recovered from a partial phenomenon to normal paradoxical sleep, had lesions intermediate in size between those of KH3 and those of the other cats (Fig. 1).

It is more difficult to relate the severity and longevity of the phenomenon to the location of the lesion, especially with regard to the relative involvement of the locus coeruleus versus the classical reticular formation. Although the lesion in KH4 was heavily centered in the locus coeruleus at all levels, it also involved the reticular formation medio-ventral to it. All the other large lesions involved the reticular formation to the same degree that they damaged the locus coeruleus. It is of interest that of the three animals with smaller lesions, KH5, who was the least affected in paradoxical sleep, showed the heaviest damage of the locus coeruleus.

Behavior during wakefulness following pontine lesions

Of the cats having paradoxical sleep without atonia KH1 was least disturbed in her wakeful behavior. On the 1st postoperative day she ate, urinated and, except for a slight stumbling to the right, walked normally. KH3 showed similar behavior. The other cats initially exhibited severe motor deficits characteristic of cerebellar damage, such as opisthotonus, forelimb extensor hypertonus, ataxia, atonic bladder and aphagia. These signs gradually diminished in severity over a period
of a week or so. All of these cats had varying degrees of ataxia, tremor and severe alterations of muscle tone, but were otherwise in good health when sacrificed for examination of the lesions.

**DISCUSSION**

The results described above indicate that the dorsolateral tegmentum of the pons is necessary for muscular atonia during paradoxical sleep. When this area is destroyed to some critical extent, permanent release of organized motor behavior will appear during that state. Abolition of the atonia of paradoxical sleep was linked with apparent absence of rapid eye movements. One problem to be considered in evaluating the results is how can paradoxical sleep be determined in the absence of two of its main criteria, i.e., atonia and rapid eye movements? The following observations support the notion that the episodes described above were episodes of paradoxical sleep:

1. The electrical activity of the cortex consisted of high-frequency, low-voltage waves characteristic of wakefulness and paradoxical sleep.

2. The animals were clearly asleep during these episodes as evidenced by miotic pupils, relaxed nictitating membranes and the fact that they could be awakened by the usual arousing stimuli, such as a sound or pinch. On awakening, the pupils dilated, the nictitating membranes retracted, and the cats began to orient to visual stimuli. Their movements, although still ataxic due to cerebellar damage, became more coordinated when awakened. In the case of KH1 the movements were essentially normal when the cat awakened. Rather than remaining awake, the cats frequently stretched, yawned, curled up and entered the synchronized phase of sleep.

3. In all cats the episodes followed periods of synchronized sleep, in which there had been a gradual diminution of muscle tone.

4. The waxing and waning of the movements closely paralleled the pattern of twitches and quiescence characteristic of normal paradoxical sleep (6). In both cases, bursts of activity alternate with periods of rest and grow increasingly strong as the period progresses. Although experimental proof is lacking, we would suggest that during the more violent movements rapid eye movement bursts also occurred. Rapid eye movements normally occur in conjunction with the often vigorous facial and distal limb twitches in the normal cat (6) so that it would be reasonable to suppose that they were masked by the violent movements of cats in the present study. The alternative, that eye movements were eliminated by the lesion, seems unlikely since only lesions of the vestibular nuclei have been shown to abolish rapid eye movements (23);
and lesions in the present case did little damage to the most direct connection between the vestibular and various oculomotor nuclei, the medial longitudinal fasciculus, destruction of which appears to have a minor effect on rapid eye movements in any event (21).

5. Except for the transition to recovery in three cats, episodes of normal paradoxical sleep were never interspersed with abnormal ones.

6. In three cats the episodes recovered fully or partially into episodes of clear paradoxical sleep with atonia and eye movements.

Other, more speculative factors, are also in favor of the hypothesis. The movements observed during paradoxical sleep without atonia are highly reminiscent of those induced by stimulation of the reticular formation, or fastigial nuclei (26, W. W. Chambers and J. M. Sprague, personal communication). We might now ask if there are any events taking place in the nervous system during paradoxical sleep which could lead to movements simulating those induced by electrical stimulation. Indeed there are, for various investigations of the firing patterns of single neurons (e.g., 2, 5) have shown that in paradoxical sleep units discharge in long bursts interrupted by intervals of inactivity. A more regular pattern of firing is seen in wakefulness. Moreover, Evarts (5), working with unanesthetized monkeys chronically prepared for single-unit recording, has demonstrated that neighboring units, which normally fire reciprocally with wrist flexion or extension when the monkey is awake, discharge in unison during paradoxical sleep. To quote Evarts, “one may presume that with the extremely intense PT (pyramidal tract) bursts characteristic of sleep with low voltage, fast activity the output which descends via the pyramidal tract resembles that set up by *electrical stimulation or strychninization* (authors’ emphasis) of the cortex.” Also, he states, “We may thus see that both sleep with low voltage, fast activity and waking involve the occurrence of movements but that the pattern of neuronal discharge underlying the two sorts of movements is quite different, the movements of sleep with low voltage, fast activity probably depending on massive high frequency discharge of a type which does not ordinarily occur in the normally functioning brain during waking”. The movements during paradoxical sleep of which Evarts speaks are the muscular twitches which are particularly frequent in the flexor muscles of the distal extremities (6). If one assumes that the α-motor neurons are freed of an inhibitory input as a result of the pontine lesion, presumably due to defacilitation of the inhibitory reticular formation (16), then it would be reasonable to suggest that descending facilitatory volleys, which normally are only able to bring some of the motor neurons to firing level in order to produce twitches, are playing down upon the motor neurons during paradoxical sleep.
without atonia in a manner similar to that seen with electrical stimulation. Although stimulation of a point of motor cortex or other centers produces only isolated fragments of movements, there is ample evidence that many motor systems are active during paradoxical sleep and therefore capable of evoking movements were the motor neurons not inhibited (22). Thus the motor activities observed during paradoxical sleep without atonia might be viewed as the expression of poorly regulated movements as well as more complex behavior patterns which are normally hidden from the experimenter's eye by the barrier imposed by the widespread inhibition of the motor neurons (7, 20).

Therefore, the interpretation of this experiment is that paradoxical sleep remains and is still triggered after lesions of the dorsolateral pontine tegmentum. Furthermore, the recent finding from this laboratory (18) that interruption of inhibitory fibers ascending from the caudal spinal cord eliminates atonia in paradoxical sleep to the extent that cats will raise and bob their heads as well as move their entire forelimbs argues for the notion that interruption of some combination of fiber pathways within the reticular formation, rather than destruction of specific nuclei, was responsible for the lack of atonia observed in the present study. The conclusion to be drawn from the former study (18) is that removal of a portion of the fiber input to the reticular formation (24) reduced the efficiency of the mechanism producing atonia in paradoxical sleep, whatever that mechanism might be.

How do the results and conclusions of the present experiment compare with those of other authors? The idea that the locus coeruleus and the surrounding reticular formation are responsible for atonia during paradoxical sleep is not new. In 1965, Jouvet and Delorme reported that lesions of the locus coeruleus produce paradoxical sleep without atonia (14). Their description of the phenomenon agrees in essential aspects with the present one. Roussel (25) from the same laboratory observed similar behavior with such lesions. Thus, we have confirmed their earlier reports that lesions of the pontine tegmentum will eliminate atonia in paradoxical sleep. In addition they noticed that PGO waves were present during these episodes. Since the work of Roussel (25), however, it has been emphasized that lesions of the dorsolateral tegmentum, specifically the nuclei of the locus coeruleus and the reticular formation medioventral to them, produce total and selective suppression of paradoxical sleep itself, and therefore, that paradoxical sleep depends upon 'trig-gering' mechanisms located in the locus coeruleus' (12). This re-interpretation rests on the evidence that the cats in the original Jouvet and Delorme experiment, and that of Roussel, showed total suppression of paradoxical sleep for a period of 15 to 20 days before they exhibited...
paradoxical sleep without atonia. We have never observed such a postoperative lag in the appearance of paradoxical sleep without atonia. KH4, who was not observed until the tenth postoperative day, may have had such a suppression. On this we cannot comment, but the full development of paradoxical sleep without atonia when KH4 was first observed and its permanence suggests the phenomenon to be the specific effect of this lesion. KH12, we should add, had a similar lesion. Even the delay of 3 or 4 days seen in KH12 and KH2 with large lesions consisted of poorly defined episodes of sleep and wakefulness. In this regard the most impressive results were obtained with KH1, who exhibited immediate recovery from anesthesia and surgery and well-defined episodes of paradoxical sleep without atonia as well as essentially normal wakefulness. Furthermore, the results obtained with the lesion in KH1 argue against the recent idea that it is only the caudal portion of the locus coeruleus which is involved in the maintenance of atonia of paradoxical sleep (13). In this cat the locus coeruleus was barely involved at all. KH6, who only recovered partial atonia after several months, also had a rather small lesion.

We have some observations to make on the difference in time of onset of paradoxical sleep without atonia in our experiments and those quoted above. One might argue that we just did not involve enough of the locus coeruleus. However, Roussel (25), who reported total suppression of paradoxical sleep for as long as 15 to 20 days before observing the hallucinatory phenomena, had some lesions similar to ours, three of which damaged as little as 9, 13 and 25% of the locus coeruleus, yet led to total abolition of paradoxical sleep for over 12 days survival (see his Planche 5). These cats may have been similar to KH4, if she really were without paradoxical sleep when not observed. The lesions of Roussel's animals kept long enough to exhibit paradoxical sleep without atonia were not illustrated. Roussel's illustrated lesions which destroyed large portions of the locus coeruleus also involved the brachium conjunctivum, a major outflow of the cerebellum, and the vestibular nuclei. Although damage of these structures alone does not prevent appearance of paradoxical sleep (9, 10, 23, 25), this does not say that combined lesions of this area would not have serious effects on paradoxical sleep. However, this statement is not particularly satisfying unless one views the problem as one of motor control. Prior to developing paradoxical sleep without atonia, cats in the Jouvot and Delorme (14) and Roussel (25) experiments terminated periods of synchronized sleep with an abrupt jerk of the head and neck into hyperextension, which resulted in arousal. Our cats with larger lesions also demonstrated this behavior to excess in the first 10 postoperative days. Rather than suggesting to us
that the triggering mechanism of paradoxical sleep was destroyed, this
observation indicates that the cats were stimulated to arousal from
paradoxical sleep with the sudden unusual increase of neck muscle tone
at a time when atonia should have begun. As the cats' nervous system
recovered motor control during wakefulness to the extent that they could
walk about, so the unusual onset of increased muscle tone at the end of
synchronized sleep became sufficiently regulated, so that the head rose
gradually rather than abruptly; and the cats could remain in paradoxical
sleep without atonia rather than being immediately aroused (15 days
recovery time in both cases in Roussel's experiments). Morrison and
Bowker (19) found that even after partial lesions of the vermal cere-
bellar cortex the transitional period with PGO waves prior to paradoxic-
al sleep onset was characterized by strong extensor jerks of the neck
and forelimbs, although these cats eventually entered paradoxical sleep.
KH1, on the other hand, essentially normal in her motor control during
wakefulness, had episodes of paradoxical sleep without atonia immedia-
tely. Following this line of reasoning, one is forced to the conclusion
that in the early postoperative period pontine lesions lead to poor regu-
lation of motor functions in both wakefulness and paradoxical sleep and
to a defect in maintenance of the latter rather than triggering.
Roussel's lesions damaging a small portion of the locus coeruleus yet
abolishing paradoxical sleep invaded the nucleus subcoeruleus and the
dorsolateral portion of nucleus reticularis pontis caudalis (also oralis in
our estimation) and, therefore, these nuclei were included as structures
necessary for the paradoxical sleep mechanism. This conclusion leads
us to recall the results of Jouvet's earlier pioneer study (10), which in-
volved large lesions of the nucleus reticularis pontis oralis and caudalis
and the locus coeruleus and appear to have included the lesion-sites of
the Jouvet and Delorme (14) and Roussel (25) studies. These early lesions
were also interpreted as leading to complete abolition of paradoxical
sleep, and this statement is still cited in the literature as evidence that
the pontine tegmentum is crucial for paradoxical sleep. However, the ani-
imals showed, as early as 3 days postoperatively, periodically occurring
"hallucinatory-like" behavior, the description of which is similar to the
description of paradoxical sleep without atonia in the later studies (14,
25) and in the present report. Of course, the present-day interpretation
of this "hallucinatory" behavior as paradoxical sleep without atonia
means that those large lesions of the pontine tegmentum led not to
total abolition of paradoxical sleep, but only to abolition of the atonia
of paradoxical sleep. If one suggests that these extensive lesions did not
involve enough of the locus coeruleus to prevent paradoxical sleep, this
suggestion would support our hypothesis that it is damage of a combi-
nation of nuclei and pathways in the tegmentum which produces paradoxical sleep without atonia.

Carli and Zanchetti's (3) report that they did not affect paradoxical sleep in any way with lesions involving the locus coeruleus, including atonia, which led them to the conclusion that these nuclei play no essential role in regulating any of the aspects of paradoxical sleep, remains to be explained. Their lesions were more laterally placed and left out the medioventral part of what is here defined as the locus coeruleus and reticular formation. Thus their lesions might not have involved to a critical extent the region held responsible here for paradoxical sleep without atonia.

Carli and Zanchetti also reported in the same study that lesions of the reticular formation of the rostral pons and caudal mesencephalon led to total abolition of paradoxical sleep. The abolition lasted for as long as 21 days (the longest period in this series) in one cat following lesion of the area. This cat also showed a most severe reduction of slow sleep so that on some days only waking activity was recorded. In fact, all animals in which paradoxical sleep had been abolished (duration 4 to 8 days) also showed a conspicuous decrease of slow sleep. The midline nuclei were heavily involved in their experiment and lesioning of these nuclei (15) as well as a midline split of the brain stem (17) is known to lead to behavioral insomnia. Paradoxical sleep only appears if a critical level (15–20%) of synchronized sleep occurs (15). Thus Carli and Zanchetti could not, and did not, claim to have abolished paradoxical sleep selectively.

An additional point to mention is that with the discovery of paradoxical sleep without atonia, proof that no brain-stem structures below the level of the pons are critical for the appearance of paradoxical sleep no longer exists. This idea was based on the finding by Jouvet (10) that two cats with caudal pontine transections, which he kept alive for more than 1 week, exhibited no periods of muscular atonia as did cats with more rostral transections. Because small pontine lesions have now been shown to block atonia in paradoxical sleep, absence of atonic episodes in caudal pontine animals can not serve to prove that they lack paradoxical sleep.

Hence, the evidence presented thus far suggests that although the caudal brain stem — or pathways crossing through it — are of crucial importance for sleep in general, and paradoxical sleep in particular, the hypothesis that a region exists within the pons exclusively concerned with the triggering of paradoxical sleep requires re-evaluation. Furthermore, our evidence indicates that damage of the locus coeruleus is probably not the important factor in production of paradoxical sleep.
without atonia. Not to be overlooked in discussions of which structure is or is not critical for appearance of paradoxical sleep or of atonia, however, is the fact that pontine tegmental lesions are capable of permanently abolishing a fundamental aspect of paradoxical sleep, muscular atonia. Although more detailed studies of the physiological and emotional status of such animals are required, their apparent good health throughout their survival periods in this study indicates that atonia in paradoxical sleep is not an indispensable aspect of this state or of life.

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