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VESTIBULAR INFLUENCES DURING SLEEP

VI. VESTIBULAR CONTROL OF AUTONOMIC FUNCTIONS DURING THE RAPID EYE MOVEMENTS OF DESYNCHRONIZED SLEEP

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VI. VESTIBULAR CONTROL OF AUTONOMIC FUNCTIONS DURING THE RAPID EYE MOVEMENTS OF DESYNCHRONIZED SLEEP[1]

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INTRODUCTION

It has long been known that sleep is associated with changes in vegetative functions. For example, the arterial pressure (62, 97) and the heart rate (11, 62) decrease to some extent during sleep, both in experimental animals and in man.

Following the demonstration that sleep can be divided into a synchronized phase, characterized by low-frequency, high-voltage electrocortical activity, and a desynchronized phase, characterized by low-voltage, high-frequency cortical activity (20), bursts of rapid eye movements (REM: 20, 56), and atonia of the posterior cervical muscles (56), several reports appeared which have dealt with various aspects of cardiovascular function during the different phases of sleep.

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[1] A preliminary report has been published (72). An account of this work has been presented by one of us in New York at the A.R.N.M.D. Meeting on *Sleep and altered states of consciousness* (79). This investigation was supported by PHS research grant NB 07685-01, from the National Institute of Neurological Diseases and Blindness, N.I.H., Public Health Service, U.S.A. and by research grant n. 69.01076-115.2857, from the Consiglio Nazionale delle Ricerche, Italy.

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Most groups of investigators (12, 16, 23, 27, 28, 33, 42, 43, 44, 45, 51, 56, 57, 58, 60, 98) agree that only a slight decrease in both arterial pressure and heart rate occurs in experimental animals, particularly in cats, during synchronized sleep. On the other hand, a marked tonic fall in blood pressure of 20 to 30, and sometimes 40 mm Hg, is generally observed during the recurrent episodes of desynchronized sleep. These effects occur not only in normal, but also in renal hypertensive cats, three to four weeks after bilateral constriction of the renal arteries (102). The marked fall of blood pressure during desynchronized sleep was generally found to be associated with a fall in the heart rate (5, 27, 28, 43, 44, 51, 56, 58, 98) although an increase in heart rate was sometimes reported by several authors (51, 56, 58, 98, 101). The tonic vegetative changes which affect the cardiovascular system parallel the well known EEG desynchronization with flattening of the cervical EMG, characteristic of desynchronized sleep. However, superimposed upon this tonic depression of arterial pressure, short-lasting, but occasionally quite marked phasic oscillations of arterial blood pressure and heart rate are often recorded. Observations made originally by Gassel *et al.* (27, 28) clearly indicated that these phasic changes in blood pressure and heart rate were related in time with the bursts of REM which occur at random during desynchronized sleep. In particular two kinds of cardiovascular events are seen during the periods of REM: i) an inconstant and slight acceleration of the heart rate, sometimes associated with an abrupt increase in blood pressure, which occurs at, or immediately precedes, the onset of the bursts of REM, and ii) a prominent fall of blood pressure and a marked slowing of the heart rhythm, which appear near the end of the train of REM and last for several seconds afterwards. These workers also found that the more intense the REM bursts, the more profound was the fall in pressure.

Later investigations have confirmed that such phasic cardiovascular changes occur during desynchronized sleep (5, 33, 43, 44, 45, 51, 59, 61, 98). In some instances pressor rises in blood pressure and heart rate followed by transient depressor troughs were found to be correlated with the bursts of REM (44, 61, 98) as reported by Gassel *et al.* (27, 28). At other times, however, such a correlation could not be made (33, 44). The negative results can be explained by the fact mentioned above that phasic changes in blood pressure and heart rate generally occur during the large bursts of high frequency REM and not during the isolated ocular jerks or the bursts of low frequency ocular movements (27, 28). This indicates that phasic vegetative changes are generated by mechanisms of temporal summation similar to those responsible for the appearance of the bursts of REM. The observation that the bursts of REM as well as the related changes in blood pressure and heart rate vary in amount and intensity during the different episodes of desynchronized sleep might explain the contradictory finding that the mean value corresponding to the heart rate may either decrease or increase during desynchronized sleep.

Changes in blood pressure and heart rate do not represent the only vegetative event which occurs during desynchronized sleep. That portion of the autonomic nervous system, which controls the pupillary diameter, is also clearly affected during this phase. It has been shown in the cat that the pupil, which is partially myotic during synchronized sleep, becomes completely fissurated during desynchronized sleep (56, 57). Moreover, superimposed on these tonic changes, transient changes in pupillary size occur during desynchronized sleep even in blind cats. They are characterized by the appearance of slight mydriatic events, which are clearly related in time with the bursts of REM (7, 49, 54, 55, 99). As is the case with the cardiovascular changes mentioned above, alterations in pupil diameter are most evident during large bursts of REM and may even be absent with small bursts.

The distinction between tonic and phasic events which affect functions in the autonomic sphere during desynchronized sleep can be applied to several somatosensory functions, which also show tonic and phasic changes during this phase of sleep. The phasic changes are related in time with the bursts of ocular movements. The literature on the tonic and phasic changes in somatosensory functions during the desynchronized phase of sleep has been reviewed elsewhere (77-81). Of specific relevance to the present study are the results of recent experiments showing that: i) the neurons located in the medial and descending vestibular nuclei discharge at high frequency during the REM periods of desynchronized sleep (9, 10) and ii) bilateral destruction of the vestibular nuclei abolishes the large bursts of REM (82, 83).

The possibility therefore existed that the transient events affecting both the somatic and the vegetative sphere during the REM of desynchronized sleep were due to the bursts of high frequency discharge originating from the second order vestibular neurons. Indeed, experiments of selective lesions of the vestibular nuclei have shown that not only the REM, but also all the phasic changes tested thus far affecting somatosensory functions during these phasic bursts of REM depend upon the activity of the vestibular nuclei (17, 74, 75, 84, 85, 86). Following bilateral destruction of the second order vestibular neurons localized in the medial and descending vestibular nuclei, various phasic events were eliminated.

The aim of the present experiments was to localize the central structures which are responsible for the phasic vegetative changes related in time with the bursts of REM. To accomplish this the heart rhythm and the pupillary diameter were monitored in unrestrained, unanesthetized cats before and after vestibular lesion. It will be shown here that the increase in discharge of the vestibular neurons that occurs during the REM periods of desynchronized sleep is also responsible for the phasic increase in heart rate and pupillary diameter which appears during the large bursts of REM. However, the tonic vegetative changes which are unrelated with the large bursts of REM can still be observed following bilateral lesion of the vestibular nuclei.

METHODS

The experiments were performed on 8 unrestrained, unanesthetized cats. Electrodes for recording the electroencephalogram (EEG), the electromyogram (EMG) of the dorsal cervical muscles, and ocular movements (electro-oculogram) were chronically implanted under Nembutal anesthesia. Two electrodes placed subcutaneously, one on the hindlimb and one on the neck, were used to record the electrocardiogram (EKG). The type of electrodes used as well as the technique of implantation have been previously described (87).

Recording sessions began two days after the operation, *i. e.*, when the effects of the barbiturate narcosis had worn off.

In order to study the changes in pupillary diameter and the ocular movements during desynchronized sleep, a plastic tubular device was used for displacing the eyelids and observing the pupils (7, 29). It was applied to one eye of the cat either at the time of the original operation or in the awake animal 1-2 hours before the recording session. Two cats were blinded bilaterally by photocoagulating the optic disks (7, 29). The unblinded cats were observed in complete darkness with the aid of a sniperscope provided with an infrared source (7, 29). Observations were continued for 2 to 48 days after chronic implantation of the electrodes and visual deafferentation. In order to analyze the time relationship between phasic vegetative changes and phasic somatic events occurring during desynchronized sleep, the pyramidal activity was recorded with bipolar electrodes just rostrally to the *decussatio pyramidum* following a method described previously (2). With this technique the pen deflections are proportional to the root mean square of the voltage between the recording electrodes. The area underneath the curve is therefore proportional to the energy of the recorded activity in the explored region.

After several recording sessions made in the intact preparation, bilateral electrolytic destruction of the vestibular nuclei was made under Nembutal anesthesia by means of stereotaxically oriented electrodes. Details of the surgical approach used for these lesions have been given elsewhere (82, 83). Recording sessions were started again 36-48 hours after the vestibular lesion and were continued for as long as 4 days after this operation.

The location of the chronic vestibular lesion was determined at the end of the experiment on serial histological sections, stained alternately with Nissl's and Weil's techniques. The delimitation of the vestibular nuclei proposed by Brodal and Pompeiano (14) was adopted.

RESULTS

1. *Changes in heart rate occurring in intact cats during desynchronized sleep.* — As noted in the introduction changes in heart rate occur in normal cats during the sleep-waking cycle. The heart rate remained rather steady during quiet wakefulness and synchronized sleep (Fig. 1 *A*, *C*) and increased during arousal. Some variation of the heart rate, however, occurred during desynchronized sleep (Fig. 1 *B*, *D*, *E*). It appears from this figure that the range of variability, which was rather small during quiet wakefulness and synchronized sleep, markedly increased during desynchronized sleep (5, 44). The great variability of heart rate during desynchronized sleep was mainly due to the pronounced phasic changes which were closely associated in time with the bursts of REM (27, 28). A calculation of the mean value would be misleading, since the number and the intensity of these bursts of REM as well as the related changes in heart rate occurring during desynchronized sleep vary from cat to cat according to the time intervening between recovery from anesthesia and the recording session, and also in the same experiment from one episode to the other.

We agree with most of the authors mentioned in the introduction that in spite of the wide range of variations, the heart rate was tonically decreased during desynchronized sleep as compared to the synchronized phase. In some instances, however, the mean value did not change significantly during the shift from synchronized to desynchronized sleep. In the experiment illustrated in Fig. 1, for instance, the mean value of the heart rate recorded during 20 episodes of desynchronized sleep was 110/min, while the value obtained during the episodes of synchronized sleep preceding the desynchronized phase corresponded to 104/min.

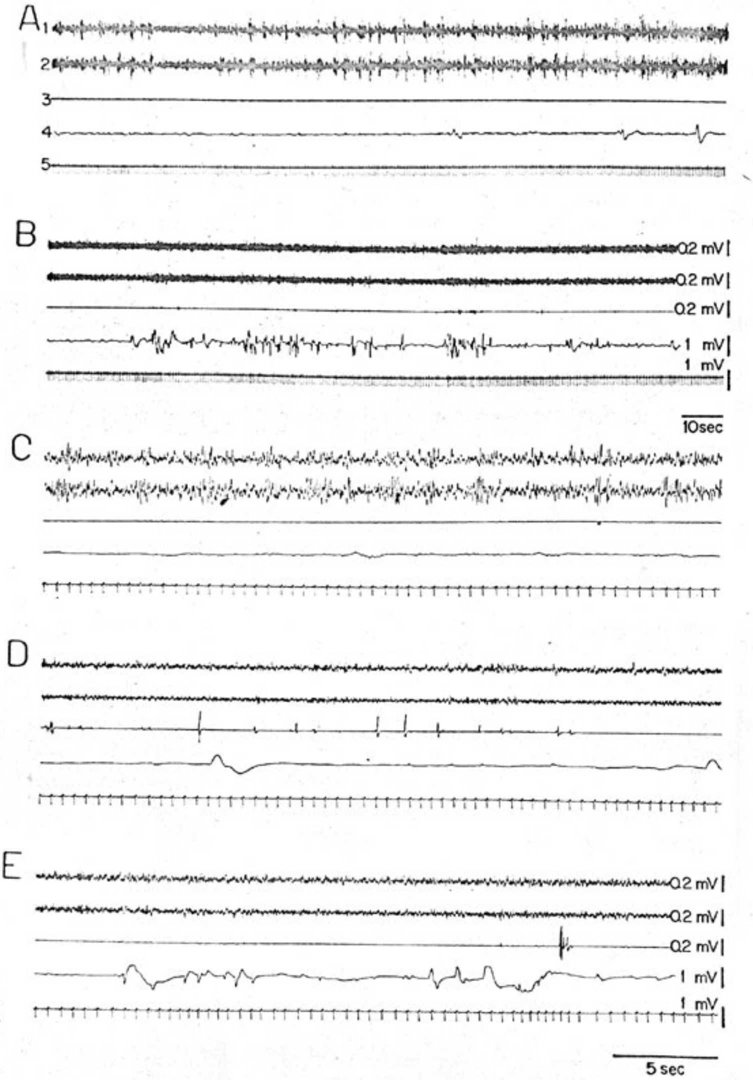

Fig. 1.

As described by Gassel *et al.* (27, 28) the most prominent changes of the heart rate occurred during the most intensive bursts of REM. The changes were characterized by an increase in heart rate which occurred at or immediately preceded the beginning of a REM burst. The acceleration of the heart rate was generally followed by a bradycardia (Fig. 1 *B*, *E*). Only in some instances was the slowing in heart rate so slight that recording with high paper speed was needed to detect alteration in the rate.

It is of interest that if the burst of REM appeared while the electro-oculogram was silent, the tachycardia occurred suddenly and was generally closely related in time with the beginning of the REM. On the other hand, when the typical burst of REM was preceded by isolated ocular jerks or when a prolonged train of low frequency ocular movements appeared in the electro-oculogram, the acceleration of the heart rate appeared gradually and one gained the impression that the tachycardia indeed preceded the appearance of the typical burst of high frequency REM.

As mentioned by Gassel *et al.* (27, 28) the relationship of this phasic vegetative change to the typical episodes of REM was a common observation. Usually, the more intense the REM bursts, the more profound were the changes in heart rate.

The close relationship between tachycardia and bursts of REM indicate that a common central mechanism is involved. Since not only vegetative, but also somatic effects occur during the most intensive bursts of REM, experiments were performed to find out whether both effects appeared simultaneously.

The integrated pyramidal discharge was chosen since it had been shown previously that the increase in the activity of the pyramidal tract which occurs during desynchronized sleep (22) is related in time with the ocular activity (67, 73). Fig. 2 clearly shows that the phasic increases in heart rate which occur during desynchronized sleep at the time of the bursts of REM are closely associated with large phasic increases in the pyramidal discharge and both are coincident with, or may precede by 1-2 seconds, the appearance of the typical burst of REM.

The phasic increases in the heart rate during desynchronized sleep do not depend upon the muscular twitches which may occur at the time of the REM since: i) they can still be observed in the absence of twitches (Fig. 2 *B*, *C*); ii) they are more long-lasting than these muscular twitches (Fig. 2 *C*) and finally iii) they can still be

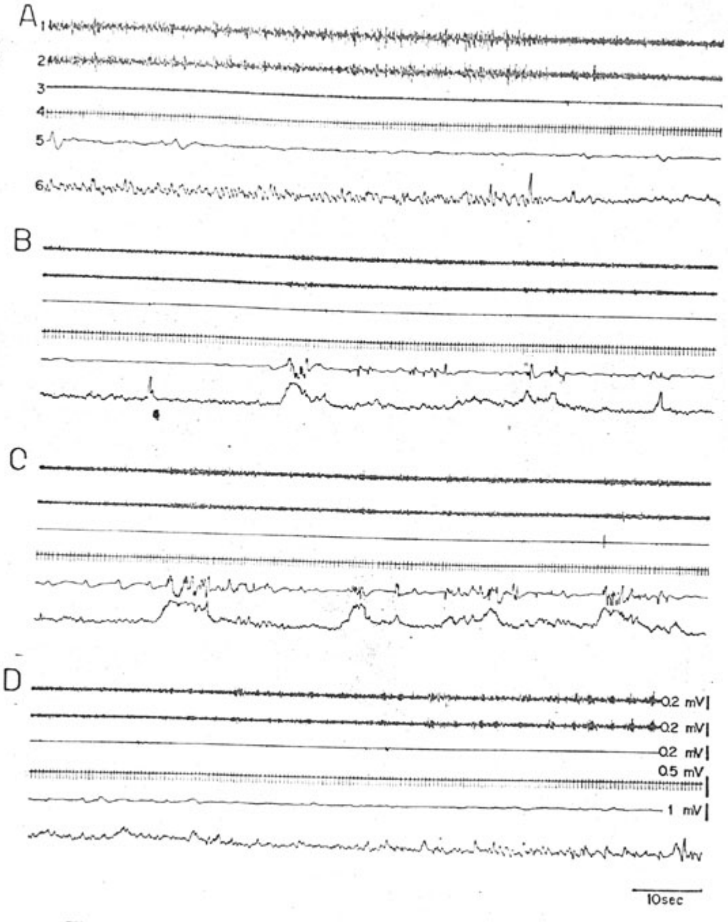

Fig. 2. – *Correlation between somatic and vegetative changes during the REM of desynchronized sleep.*

Same cat as in Fig. 1. Experiment made 48 days after the chronic implantation of the electrodes. Bipolar records. 1: left parieto-occipital; 2: right parieto-occipital; 3: posterior cervical muscles; 4: EKG; 5: ocular movements; 6: pyramidal integrated record.

A: synchronized sleep. *B*, *C*: desynchronized sleep. *D*: transition from

observed after bilateral section of the dorsal half of the lateral funiculi, which interrupts the supraspinal descending pathways responsible for these muscular contractions (79).

It can be concluded that the phasic changes in heart rate, as well as the phasic increase in pyramidal discharge occurring during desynchronized sleep, depend upon the same central mechanism which leads to the appearance of the typical bursts of REM.

2. *Selective abolition of the phasic changes in heart rate during desynchronized sleep following lesion of the vestibular nuclei.* — After complete bilateral destruction of the vestibular nuclei, the desynchronized phase of sleep was still characterized by the so-called tonic manifestations, such as the desynchronization of the electrocortical activity and the complete relaxation of the posterior cervical muscles. However, the typical bursts of REM (82, 83), as well as the phasic increases in pyramidal discharge (74), were abolished by the lesion. After complete destruction of the vestibular nuclei, the heart rate was generally higher during quiet wakefulness and synchronized sleep with respect to the control values taken in the same experimental conditions before the lesion. The increase was generally of the order of 20%.

Although the lesions in the present study were placed within the vestibular nuclei and outside the confines of the medullary cardiovascular center, one could argue that the increase in the heart rhythm observed after vestibular lesion might be due to involvement of the basic mechanism regulating cardiovascular function rather than lack of vestibular function. Judging from the EKG records obtained during wakefulness and synchronized sleep, however, cardiovascular

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Fig. 1. – *Phasic changes in heart rate during desynchronized sleep.*

Unrestrained, unanesthetized cat. Experiment made 48 days after the chronic implantation of the electrodes. Bipolar records. 1: left parieto-occipital; 2: right parieto-occipital; 3: posterior cervical muscles; 4: ocular movements; 5: EKG.

A, *C*: synchronized sleep. *B*, *D*, *E*: desynchronized sleep. Note the regularity of the heart rate during synchronized sleep and the great variability of the heart rate during desynchronized sleep.

Most of the intensive bursts of REM in *B* and *E* are usually accompanied by an increase in heart rate, which is followed by a bradycardia outlasting the REM burst for several seconds.

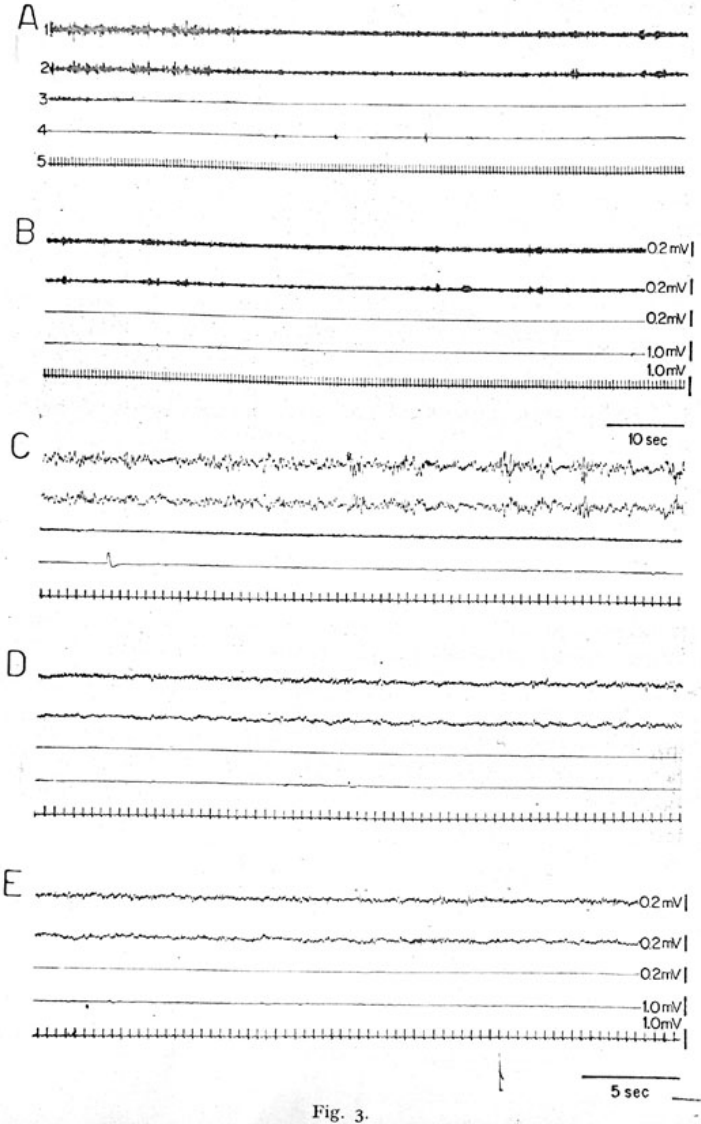

Fig. 3.

activity was essentially normal at these times. Also normal increases in heart rate were seen during the arousal reaction.

Contrary to the intact preparation, the heart rate was very regular and the range of variability was rather small during desynchronized sleep (Fig. 3), as well as during both quiet wakefulness and synchronized sleep. Moreover, no significant change could be found in the heart rate during the shift from synchronized to desynchronized sleep. In the experiment illustrated in Fig. 3 the mean value of the heart rate corresponded to 131/min during synchronized sleep and to 127/min during the desynchronized phases. The most striking finding of our experiments, however, is that the usual phasic changes of the heart rate observed in conjunction with REM in normal cats did not appear after vestibular lesion (Fig. 3). Instead of the usual bradycardia which normally ensues near the end of the bursts of REM and which is associated with a prior tachycardia at the beginning of the bursts, the cats with lesions exhibited a very regular heart rhythm for the duration of the desynchronized episode.

The abolition of the phasic changes in heart rate during the REM periods of desynchronized sleep was observed whenever the lesion was bilateral and affected the vestibular nuclear complex in its entire rostro-caudal extent. Bilateral electrolytic lesions limited to the medial and descending vestibular nuclei were equally effective. On the other hand, when the lesion involved the two vestibular nuclei only partially or unilaterally, REM were present but reduced in number and duration. The phasic changes of the heart rate still occurred after these incomplete lesions.

3. *Pupillary changes occurring in intact cats during desynchronized sleep.* — The previously described changes in pupillary diameter (7, 49, 54, 55, 99) that are seen in desynchronized sleep, particularly those synchronous with bursts of REM, were first confirmed in intact animals. To review briefly, the pupils became increasingly myotic as the cat passed from quiet wakefulness to synchronized

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desynchronized to the synchronized phase. Striking phasic increases in the pyramidal activity occur during the bursts of REM, occasionally associated with neck muscular twitches (*C*). There is a close correlation between phasic increases in the pyramidal discharge and phasic changes in the heart rate, particularly during the large bursts of REM.

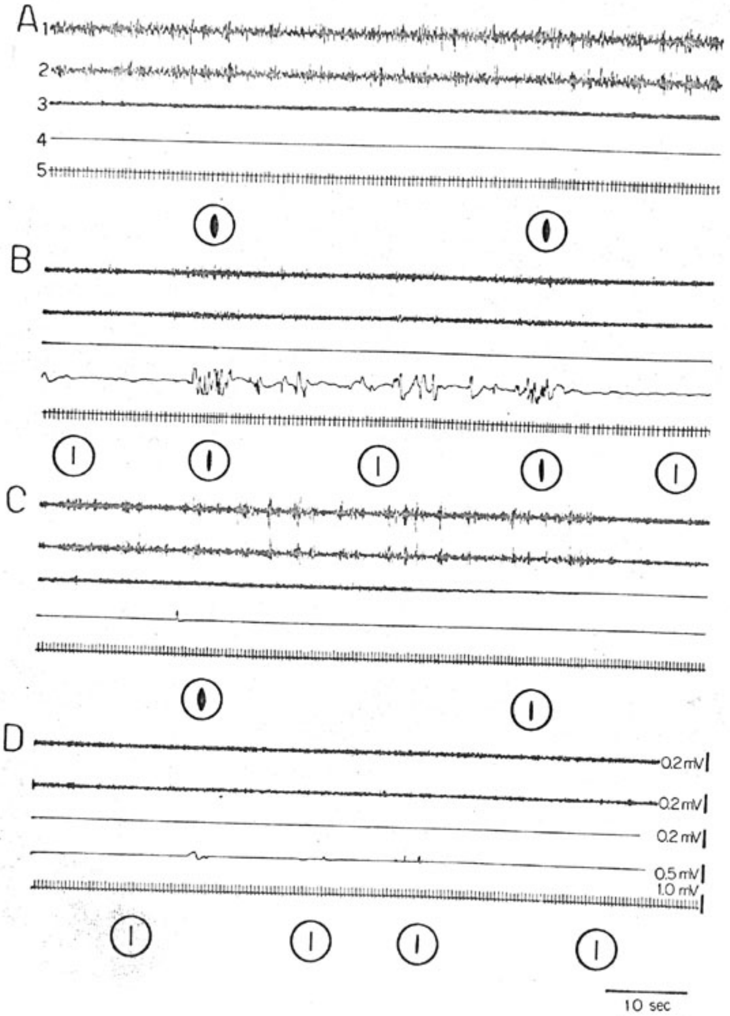

Fig. 4.

sleep. At the beginning of desynchronized sleep the pupils were completely or almost fissurated. Whenever REM intervened, however, a brief mydriasis was observed to coincide with these ocular movements (Fig. 4 *A*, *B*). The degree of dilation was related to the repetition rate of the ocular movements within the burst of REM, although the mydriatic responses of desynchronized sleep never matched the extent of pupillary dilation associated with arousal.

Fig. 4 (*A*, *B*) is also of particular interest since it shows the close relationship existing between intensity of the burst of REM, phasic increase in pupillary diameter and acceleration of the heart rate.

4. *Selective abolition of the phasic pupillary changes during desynchronized sleep following lesion of the vestibular nuclei.* — In cats in which the vestibular nuclei were bilaterally destroyed throughout their rostrocaudal extent, no differences from the pupillary changes observed in intact cats during wakefulness and synchronized sleep were noted. As in normal cats the pupils constricted tonically in the periods of transition from wakefulness to drowsiness. The myosis gradually increased as synchronized sleep progressed. When the cat reached the stage of desynchronized sleep, the pupils became fissurated (Figs. 4 *C*, *D*; 5 *A*).

As mentioned above, complete bilateral vestibular lesions prevented the appearance of the characteristic bursts of REM; only slow ocular movements and occasional isolated jerks of the eyes were noted (Figs. 4 *D*; 5 *B-D*).

The most striking finding in these experiments was the lack of the short-lasting and pronounced pupillary dilations which in

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Fig. 3. — *Abolition of the typical bursts of REM and the related phasic changes in heart rate following a vestibular lesion.*

Unrestrained, unanesthetized cat, 3 days after a complete bilateral lesion of the medial and descending vestibular nuclei. Bipolar records as in Fig. 1.

A: transition from synchronized to desynchronized sleep. *B*: continuation of the episode of desynchronized sleep. *C*: another episode of synchronized sleep, followed by a desynchronized phase (*D*, *E*).

Note the abolition of the typical bursts of REM and the related changes in heart rate during the desynchronized episodes. The vestibular lesion also abolished the great variability of the heart rate, which occurs in the intact preparation during desynchronized sleep.

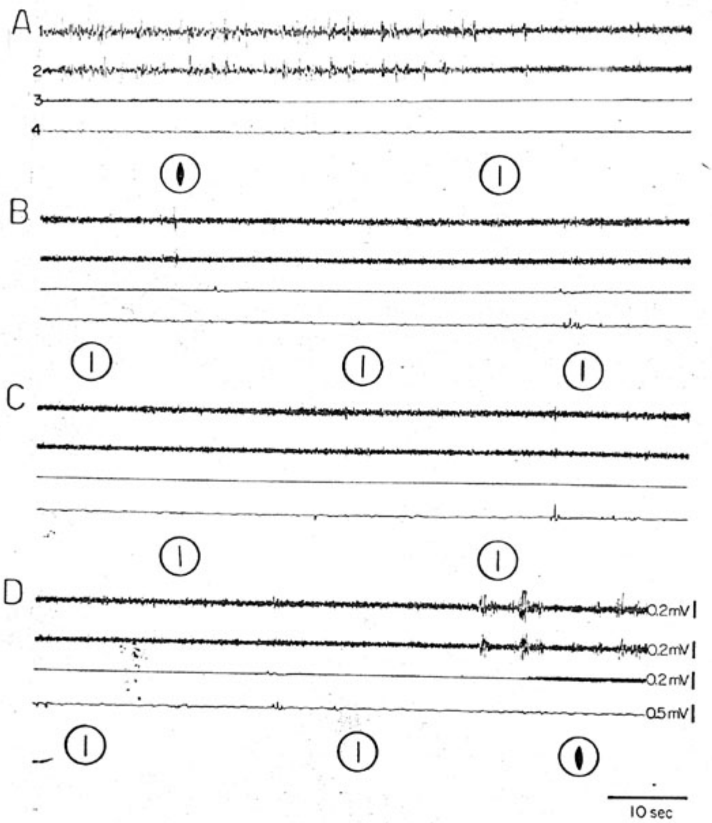

Fig. 5. – *Abolition of the typical bursts of REM and the related mydriatic responses following a vestibular lesion.*

Unrestrained, unanesthetized cat, 2 days after a bilateral lesion of the medial and descending vestibular nuclei. Bipolar records as in Fig. 1.

Reduction of the pupillary diameter during transition from synchronized to desynchronized sleep (*A*). A fissurate myosis can be observed throughout the episode of desynchronized sleep (*B-D*). A very slight pupillary dilation can be observed only in *B* during an isolated group of small ocular jerks.

the intact animal were seen in conjunction with REM. During the episodes of desynchronized sleep one saw only very slight variations in the size of the pupil. At these times the transverse diameter of the pupil would vary from a width of less than one millimeter to complete fissuration (Figs. 4, 5). The slight pupillary dilations in the lesioned cats were always related in time with remaining isolated ocular movements. Fig. 4 C, *D* is of particular interest since it shows that the fissurated pupils, which persisted almost unmodified throughout the episode of desynchronized sleep, were associated with a great regularity of the heart rate.

As was the case with the changes in heart rate during desynchronized sleep, bilateral lesions including only the medial and descending nuclei also eliminated the phasic changes in pupillary diameter during desynchronized sleep. Thus the same nuclei whose presence is required for the appearance of REM (82, 83), are also necessary for phasic pupillary changes during desynchronized sleep.

DISCUSSION

The main result of the present experiments is the demonstration that during desynchronized sleep the phasic effects in the autonomic sphere, which are related in time with the bursts of REM, depend upon the activity of the vestibular nuclei. It is of interest that a bilateral lesion of the vestibular nuclei abolishes not only the bursts of REM (82, 83), but also the cardiovascular and the pupillary changes synchronous with them. The critical region, whose destruc-

Fig. 4. – *Phasic changes in heart rate and in pupillary diameter during the large bursts of REM in the intact preparation and their abolition following a vestibular lesion.*

Unrestrained, unanesthetized cats. *A*, *B*: same experiment as in Fig. 1, same bipolar records. Pupil behavior during synchronized (*A*) and desynchronized sleep (*B*). Note the fissurated myosis during desynchronized sleep when the eyes are at rest and the pupillary dilation synchronous with two large clusters of high frequency ocular movements. The mydriasis is also associated with typical accelerations of the heart rate related in time with REM.

C, *D*: same experiment as in Fig. 3. After the vestibular lesion a fissurated myosis persists almost unmodified throughout the episode of desynchronized sleep. Note also the great regularity of the heart rate during this phase of sleep. A very slight pupillary dilation occurs only during a residual ocular jerk (in *D*).

tion is responsible for the effects described above, included the medial and descending vestibular nuclei. The lesion must be bilateral and affect these vestibular nuclei in their entire rostrocaudal extent. As pointed out in the introduction, endogenous activation of the vestibular neurons occurs during desynchronized sleep, as indicated by the appearance of prolonged bursts of high frequency discharge synchronous with the large bursts of REM (9, 10).

The present discussion will be centered: i) on the vestibular control of cardiovascular activity, and ii) on the vestibular control of the pupillary diameter.

1. *Vestibular control of cardiovascular activity during sleep.* — In order to understand the means by which the vestibular system is able to affect the cardiovascular activity during desynchronized sleep, the neural mechanisms responsible for both the tonic and phasic changes in cardiovascular functions typical of this phase of sleep should be known.

Changes in blood pressure and heart rate have been analyzed not only in intact, but also in cats with sinoaortic deafferentation (34, 35, 42, 43, 44), in sympathectomized (5, 40, 41, 98) and vagotomized cats (4, 5, 40, 41, 51, 98). It appears from these studies that the cardiovascular changes occurring during desynchronized sleep do not depend upon peripheral mechanisms.

The tonic falls of arterial pressure, and to a lesser extent the heart rate, are actually enhanced after bilateral sino-aortic deafferentation (34, 35, 42, 43, 44), an effect which has been attributed to interruption of the buffering action of reflex chemoceptive discharges (3, 36, 37, 38, 39). Even the phasic variability of arterial pressure during desynchronized sleep, which is related in time with the large bursts of REM (27, 28), does not seem to depend upon reflex modulation by sino-aortic afferents, as such variability was still present after sino-aortic deafferentation (see Fig. 6 in 44). This finding does not rule out the hypothesis that in the intact preparation vestibular volleys affect the orthodromic transmission of the visceral afferent impulses originating from the carotid bifurcation and aortic arc at presynaptic level, thus contributing to the appearance of the phasic responses during the bursts of REM[1]. At pres-

ent, one may postulate that central mechanisms are mainly, although probably not exclusively, responsible for the cardiovascular changes occurring during desynchronized sleep.

The tonic fall in blood pressure throughout desynchronized sleep was observed in both intact and vagotomized cats (4, 40, 41, 51, 98). Even the tonic reduction in the heart rate during desynchronized sleep still took place after bilateral vagotomy (5, 51, 98; cf. however 4, 40, 41). The administration of methyl-atropine had the same effects (40, 41, 51). These findings suggest that during desynchronized sleep there are decreases in both vasoconstrictor tone and cardiac facilitatory influences, which are normally maintained by a tonic discharge of the sympathetic nervous system. This conclusion is supported by the observation that a decrease in sympathetic postganglionic discharge occurs during desynchronized sleep in free-moving cats (6) as well as during the comparable episodes in decerebrate cats (52). Collateral evidence also leads to the same conclusion (53, 63, 64). However, additional parasympathetic influences can also be demonstrated. After bilateral ablation of the stellate ganglia there is still a fall in blood pressure (40, 41, 98) and heart rate (5, 40, 41, 98) during desynchronized sleep; but after complete denervation of the heart a decrease in heart rate during desynchronized sleep is no longer observed (5, 40, 41, 98).

The transient changes in blood pressure and heart rate associated with the bursts of REM occurring during desynchronized sleep are caused by changes in the sympathetic and vagal activity as well. A detailed analysis has shown, in fact, that the increase in blood pressure which corresponds to the bursts of REM is brought about by an increase in sympathetic activity since it still persisted after bilateral vagotomy or administration of methyl-atropine (51). Phasic bursts of sympathetic activity may actually occur during desynchronized sleep (6).

On the other hand, the hypothesis that the transient acceleration of the heart rate occurring at the onset of the burst of REM is due to a short-lasting fall in the vagal cardio-inhibitory tonus (27, 28) is supported by the fact that the effect was still present in stellectomized cats (5, 98), but was greatly reduced after bilateral vagotomy (5). The latter authors also observed that the following bradycardia is brought about by a phasic inhibition of the sympathetic output and a simultaneous increase in the vagal discharge.

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[1] Recent experiments indicate that the vagal and aortic low-threshold afferents are not subjected to presynaptic inhibitory control, at least from the periphery (88).

There is no doubt that these short-lasting changes in vagal and sympathetic activity depend upon the efferent discharge originating from the vestibular nuclei during the REM since they are abolished, together with the ocular movements, following bilateral lesion of these structures. After this lesion rhythmic ponto-geniculate activity still occurs (75, 85); yet the phasic changes in heart rate are completely abolished.

The observation that in some instances the phasic changes in blood pressure and heart rate precede the bursts of REM does not speak against the vestibular origin of these vegetative responses since the activity of the vestibular neurons may slightly precede the occurrence of these ocular movements (9, 10). In most of these instances, however, the acceleration of the heart rate heralding the burst of REM can be associated with very small but clearly detectable ocular movements which precede the occurrence of the typical burst of REM.

The relationship between the vestibular nuclei and the autonomic nervous system controlling the cardiovascular activity during REM sleep is probably not direct. The vestibular effects may be mediated by the brain stem reticular formation and/or the hypothalamus. This hypothesis is supported by the fact that the firing rate of cells in regions involved in this autonomic control, such as the brain stem reticular formation (10, 50) and the hypothalamus (24), is markedly affected during desynchronized sleep, particularly at the time of the sporadic phasic events.

The finding that the phasic cardiovascular changes observed during REM sleep depend upon vestibular activity is consistent with the notion that vegetative reactions can be elicited during labyrinthine stimulation. Evidence that stimulation of the labyrinth leads to cardiovascular changes is furnished by experiments of rotatory, galvanic, electric and caloric stimulation of the labyrinth (8, 32, 46, 47, 48, 66, 69, 70, 76, 92, 93, 94, 96; cf. 15, 71, 91). While the cardiovascular changes produced by experimental stimulation do not always mimic those observed during the REM bursts of desynchronized sleep, such discrepancies can probably be attributed to the modality of vestibular stimulation, the different types of preparation (decerebrate or intact preparation), and the type of anesthetic used. Suffice it to say that the vegetative reactions, which seem to originate from the semicircular canals (65, 91), are abolished by destruction or inactivation of the peripheral labyrinth (8, 46, 92, 95) or by lesion of the medial vestibular nucleus (91, 93, 94). Apparently the vestibular impulses are transmitted through the medial vestibular nucleus to the vegetative centers via the reticular formation (69, 91). There is evidence, however, that supramesencephalic structures may modify these reactions (1, 8, 19, 94). It is also of interest that the efferent vestibular volleys have a variety of effects on the parasympathetic vagal nerve (1, 19, 30, 31, 32, 68, 92) as well as on the sympathetic system (18, 19, 68).

The observation that the phasic changes in blood pressure and heart rate occur only during the large bursts of REM should be discussed now with regard to the problem of sleep deprivation. It has been clearly shown that the frequency and the amplitude of the ocular movements within the REM burst can be taken as indirect criteria of the firing level of the vestibular neurons (9, 10). Since the vegetative centers are under the control of these vestibular volleys, it is obvious that the sleep modulation of vegetative functions are more likely to occur during the large bursts of REM than during the isolated ocular jerks. Recent experiments clearly support this conclusion, for they have shown that REM sleep deprivation has a pronounced and generalized effect upon cardiac activity (61). Since after selective deprivation of REM sleep the eye movement bursts of desynchronized sleep become more intense (21), it is not surprising to find an overall increase in heart rate during post-deprivation REM episodes as a result of an increased vestibular discharge.

2. *Vestibular control of the pupillary diameter during sleep.* — The present experiments have shown that the pupillary dilations related in time with the bursts of REM are also abolished by a vestibular lesion. A dissociation, therefore, was obtained between the phasic mydriatic episodes, which occur during the REM bursts (7, 49, 54, 55, 59), and the tonic pupillary myosis (56, 57) which persists throughout the desynchronized episodes following the vestibular lesion.

The finding that, in addition to the well-established control exerted by the vestibular system over the extraocular muscles, vestibular volleys also affect the intrinsic eye muscles is supported by experiments in which the labyrinthine receptors were stimulated. Dilation of the pupils has been observed on caloric or galvanic stimulation of the ear (see 91 for references). However, rotatory labyrinthine stimulation induces a gradually increasing constriction, followed by a well-pronounced myosis and then mydriasis after the turning has ended (25, 26, 89, 100, cf. 91). Since integrity of the cervical sympathetic nerve is not necessary for this reaction (89, 90), the suggestion was put forward that the pupillary changes are brought about through transmission of labyrinthine impulses to the Edinger-Westphal nuclei, each labyrinth influencing the pupillo-constrictor centers of both sides (cf. 91).

It is of interest that the phasic mydriatic episodes which occur during REM bursts are still observed after sympathetic preganglionic denervation and are the expression of phasic inhibitions of extra-retinally driven Edinger-Westphal tonus (7). Some enhancement of the sympathetic activity is suggested, however, by the finding that the increase in pupillary diameter during REM is also associated with a contraction of the nictitating membrane (49).

Obviously the vestibular volleys must have access to the structures controlling these vegetative changes. The pathway by which the vestibular activity during REM sleep affects the pupillary centers, similarly to that which affects the cardiovascular sphere, is not a direct one, but is probably mediated by the reticular formation and the hypothalamus. It is well established that both these structures control the pupillary diameter (cf. 13, 103 for references).

In conclusion the results of the present investigations clearly indicate that desynchronized sleep *per se* represents a state of quiescent and stable vegetative function. This steady state, however, is periodically interrupted by another state which is vestibular in origin, marked by heightened and labile autonomic activity. Our findings support the conclusion that vestibular discharges produce not only oculomotor, but also vegetative responses. Although in the awake animal this increase in vestibular activity depends upon excitation of labyrinthine receptors, during desynchronized sleep the increase in the vestibular discharge is triggered by extralabyrinthine volleys (75, 85), probably originating in the pontine reticular formation (56, 57). The medial and descending vestibular nuclei, which are particularly driven by this extralabyrinthine input, are thus able to produce the bursts of REM as well as all the profound changes in autonomic activity related in time with them. These effects are probably mediated through the brain stem reticular formation and the hypothalamus.

SUMMARY

1. In the unrestrained, unanesthetized cat transient increases in heart rate occur during desynchronized sleep at the time of the rapid eye movements (REM). These increases are followed toward the end of the trains of REM by a slowing in the cardiac rhythm.

2. Other vegetative changes occur during desynchronized sleep. In particular the pupils, which become fissurated when the pattern of EEG desynchronization appears in the record of the sleeping cat, show phasic, occasionally quite pronounced, mydriatic responses during the bursts of REM.

3. A bilateral lesion of the vestibular nuclei abolished not only the typical bursts of REM, but also the phasic changes in heart rate related in time with them. As a result of this lesion the heart rate shows a great regularity during desynchronized sleep.

4. As in intact animals, the pupils, which were myotic during synchronized sleep, became fissurated when the cat reached the stage of desynchronized sleep. The most striking effect of the vestibular lesion was the abolition of the short-lasting and occasionally quite pronounced pupillary dilations which in the intact animal are correlated with the ocular outbursts. In these conditions one observed only very slight and slow variations in the tonus of the sphincter of the iris.

5. The critical region, whose destruction is responsible for the effects described above, includes the medial and descending vestibular nuclei. The lesion must be bilateral and affect these vestibular nuclei in their entire rostrocaudal extent. The medial and descending vestibular nuclei are thus critically involved in the phasic autonomic changes, which appear simultaneously with the REM periods of desynchronized sleep.

6. There is evidence from the literature that the phasic increases in heart rate and pupillary diameter associated with the bursts of REM can still be observed after sympathetic denervation of the heart and the pupil. The present observations indicate that the vestibular discharge, which leads to the appearance of the REM during desynchronized sleep, is responsible for the phasic inhibition of the parasympathetic cardioinhibitory center as well as for phasic inhibition of extra-retinally driven Edinger-Westphal tonus.

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