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BLOOD PRESSURE AND SLEEP IN THE RAT IN NORMOTENSION AND IN NEUROGENIC HYPERTENSION

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SUMMARY

1. Blood pressure was recorded in normotensive rats (114 ± 2 mmHg) and in those made hypertensive by baroreceptor denervation (135 ± 4 mmHg) during natural sleep. The different states of the wakefulness–sleep cycle were identified by analysis of the frontal electrocorticogram, the cervical electromyogram and by behavioural changes.

2. During synchronized sleep the arterial pressure in the control animals usually remained unchanged as compared to values prevailing when the rats were awake and quiet. The blood pressure usually attained higher levels in the sino-aortically denervated rats during this state.

3. Coincidently with the short episodes of electrocortical desynchronization of the synchronized sleep the blood pressure exhibited rapid oscillations. These fluctuations were greater in the rats with neurogenic hypertension where there were large pressure drops.

4. During desynchronized (REM) sleep arterial pressure underwent marked oscillations. While in the control rats the pressure usually rose, the baroreceptor-denervated rats showed a severe reduction in pressure. Arterial pressure in denervated animals became lower than that of the control rats, 106 ± 2 and 121 ± 2 mmHg, respectively.

5. We interpret these results to mean that in the rat alterations in the sensitivity of the baroreceptor reflex could be an important factor in preventing the arterial pressure from rising to hypertensive levels during synchronized sleep and from dropping to low values during desynchronized (REM) sleep.

INTRODUCTION

The two states of natural sleep, synchronized (or slow wave) and desynchronized (rapid eye-movement, REM, or paradoxical) sleep, depend on distinct neural mechanisms (Jouvet, 1967; Moruzzi, 1972) and may affect cardiovascular regulation differently. Most previous studies have

been performed in cats; a small reduction of blood pressure during synchronized sleep (Mancia, Baccelli, Adams & Zanchetti, 1971) and a marked fall during desynchronized (REM) sleep have been observed in this species (Candia, Favale, Giussani & Rossi, 1962; Gassel, Ghelarducci, Marchiafava & Pompeiano, 1964; Guazzi & Zanchetti, 1965; Iwamura, Uchino & Kidokoro, 1968; Kanzow, Krause & Kühnel, 1962; Mancia *et al.* 1971) and in monkeys (Stoyva, Forsyth & Kamiya, 1968). Phasic peaks of pressure coincidental with rapid eye movements occur during the desynchronized (REM) sleep (Candia *et al.* 1962; Gassel *et al.* 1964). Chemoreceptors may play an important role in countering the pressure drop during desynchronized (REM) sleep in the cat (Guazzi, Baccelli & Zanchetti, 1968). However, a recent study showed that in the dog a surprising elevation of blood pressure after sino-aortic denervation occurs during synchronized sleep (Ferrario, McCubbin & Page, 1969). In man, a small reduction of blood pressure is usually described during synchronized sleep (Bristow, Honour, Pickering & Sleight, 1969; Coccagna, Mantovani, Brignani, Manzine & Lugaresi, 1971; Khatri & Freis, 1967; Richardson, Honour, Fenton, Stott & Pickering, 1964; Smyth, Sleight & Pickering, 1969; Snyder, Hobson, Morrison & Goldfrank, 1964), followed by either elevation (Khatri & Freis, 1967; Snyder *et al.* 1964) or drop (Bristow *et al.* 1969) during desynchronized (REM) sleep.

Behavioural and electrophysiological aspects of natural sleep have been thoroughly studied in the rat (Roldán & Weiss, 1962; Schmidek, Hoshino, Schmidek & Timo-Iaria, 1972; Timo-Iaria, Negrão, Schmidek, Hoshino, Menezes & Rocha, 1970). Although this species has been used in almost every type of study of experimental hypertension, blood pressure changes during sleep hitherto have not been reported. Since rats are widely used in our laboratory to study neurogenic hypertension produced by sino-aortic denervation (Junqueira & Krieger, 1973; Krieger, 1964, 1967, 1970) we now describe an analysis of the blood pressure changes occurring during natural sleep in normotension and in neurogenic hypertension.

METHODS

Animals and recording. Male Wistar rats weighing from 200 to 250 g were used. Blood pressure was measured directly by means of a plastic cannula (PE10 connected to a PE50) inserted into the abdominal aorta through the femoral artery under either anaesthesia the day before the recording session. The cannula emerged through the back of the rat and was connected by a 30 cm length polyethylene tubing (PE90) to a Statham P23-Dd pressure transducer from which signals were fed into an eight-channel recorder (Hewlett–Packard model 7848A). The frequency response of the complete arterial pressure recording system was 90 Hz.

The different states of the wakefulness–sleep cycle were identified by analysis of the frontal electrocorticogram (e.co.g.), of the cervical electromyogram (e.m.g.) and

by behavioural changes (Timo-Iaria *et al.* 1970). The electrocorticogram was recorded by means of bipolar electrodes of nickel–chrome wire (100 μm in diameter) insulated except at the tips, and implanted (under ether anaesthesia) over the dura mater covering a discrete part of the frontal cortex (area 10). The electrical activity recorded from this area allows a convenient discrimination of the different phases and states of sleep (Timo-Iaria *et al.* 1970). The e.m.g. was recorded through bipolar electrodes hooked deep in the neck muscles. All the electrodes were connected to a miniature socket fixed on the skull with a fast polymerizing metacrylate. Recordings were taken 3 days after the implantation.

Neurogenic hypertension. Bilateral sino-aortic denervation, under ether anaesthesia, in a one-stage operation lasting 15–30 min was performed 1 day before the sleep study according to a technique described in detail elsewhere (Krieger, 1964).

Experimental procedure. The experiments to assess the influence of natural sleep on blood pressure usually lasted up to 6 hr during which the rat was kept in a Farakay cage at room temperature (25–30° C). The electrodes and the arterial cannula were connected to the polygraph in such a way that they did not disturb the spontaneous motor activity of the rat.

The electrophysiological and behavioural characterization of the different state of the wakefulness–sleep cycle was essentially similar to that described by others (Roldan & Weiss, 1962; Timo-Iaria *et al.* 1970), in both the control and the denervated rats. Whilst awake the rats remained quiet in a standing position or walked around the cage, or lay quietly with half-closed eyes; the electrocorticogram showed low voltage desynchronized activity and the e.m.g. disclosed intense muscular activity. During the synchronized sleep periods, lasting 10–15 min, the animals adopted a curled position, the breathing was deep and regular and the eyes were closed; the electrocorticogram displayed slow waves of high amplitude regularly interrupted by short periods (5–20 sec) of desynchronization during which the rats changed position. The e.m.g. during the synchronized sleep showed diminished muscular activity. The episodes of desynchronized (REM) sleep, lasting 1–3 min appeared usually after several periods of slow-wave sleep interrupted by short episodes (5–10 min) of wakefulness. During the desynchronized (REM) sleep the animals exhibited body relaxation, the head usually remained in ventroflexion, respiration became irregular and jerks of different parts of the body occurred. The electrocorticogram showed a low voltage fast activity and the e.m.g. indicated little or no muscular activity. Blood pressure was continuously recorded during the three states of the sleep–wakefulness cycle. Intermediate periods which were difficult to classify were not selected for study.

Expression of results. For analytical purpose, the values of the mean blood pressure (MAP) will be given as means $\pm$ S.E. of mean; differences were considered significant at the level of 5% by using the paired observations test (Dixon & Massey, 1957).

RESULTS

Normotensive rats

Records of blood pressure in the awake rats showed that it remains quite stable (114 ± 2 mmHg mean arterial pressure). Large fluctuations (20–30 mmHg) were observed only when the animal moved.

Synchronized sleep. During this period the pressure became more uniform than in the awake state, because the fluctuations produced by movements were absent. As can be seen in Fig. 1, during the short episodes of

electrocortical desynchronization coincidental with arousal of the animal at regular intervals, blood pressure fluctuated rapidly. In 72 % of thirty-two episodes of synchronized sleep studied in seven rats the blood pressure remained unchanged compared with the values prevailing when the animals were awake and quiet. In 12 % a small increase (4 ± 1 mmHg) was observed and in the remaining 16 % of the episodes a small decrease (5 ± 1 mmHg) was found. The average change of mean blood pressure considering all the thirty-two episodes studied was a statistically insignificant decrease of only 0·2 ± 0·5 mmHg.

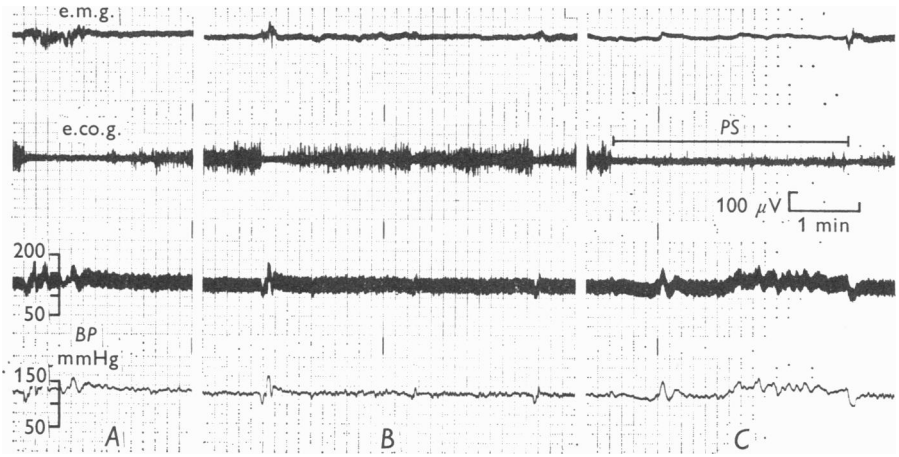

Fig. 1. Blood pressure changes during wakefulness–sleep cycle in a normotensive rat. *A*, typical record awake. *B*, pressure was more stable during synchronized sleep; rapid fluctuations coincidental with arousal (electrocortical desynchronization and increased e.m.g.). *C*, marked oscillations during desynchronized (REM, *PS* = paradoxical) sleep (electrocortical desynchronization and decreased e.m.g.). with tonic elevation in the last half of the episode. From top downwards: e.m.g., cervical electromyogram; e.co.g., frontal electrocorticogram; *BP*, pulsatile and mean pressure blood pressure.

Desynchronized (REM) sleep. In this state arterial pressure underwent marked oscillations. As shown in Fig. 1 during the first 30–60 sec of an episode of desynchronized (REM) sleep, blood pressure remained almost unchanged but thereafter tonic (40–120 sec) and phasic (5–15 sec) alterations occurred. Out of fifty episodes of desynchronized (REM) sleep observed in seven rats, 32 % presented no tonic alterations, 8 % exhibited a tonic reduction of blood pressure (4 ± 1 mmHg) and 60 % exhibited a tonic increase of blood pressure (2–15 mmHg, mean 7 ± 1 mmHg). For all the fifty episodes studied the mean change was a small (3·8 ± 0·7 mmHg)

but statistically significant tonic increase in mean arterial pressure. The phasic alterations consisted mainly of pressure rises (4–40 mmHg) and had no apparent correlation with the tonic changes. They usually appeared simultaneously with the clonic jerks and with rapid and shallow respiratory movements. Total duration of the desynchronized (REM) sleep, and the tonic and phasic changes of mean blood pressure that occurred in this

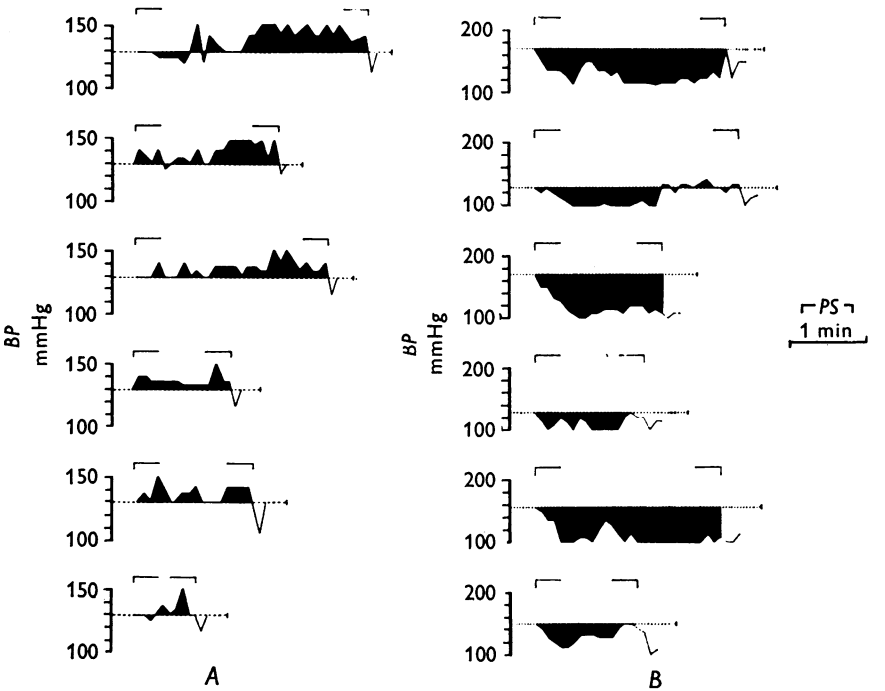

Fig. 2. Six episodes of desynchronized (REM, *PS* = paradoxical) sleep observed in a normotensive (*A*) and in a hypertensive rat (*B*). Total duration of the episodes varied from 1 to 3 min but the tonic changes of arterial pressure were uniform: an increase was seen in the normotensive rat and a decrease in the rat with neurogenic hypertension. The episodes of desynchronized (REM) sleep are indicated by the interrupted line above the blood pressure tracing.

phase are correlated in Fig. 2 in which six episodes studied in the same rat are described. In this Figure, as in Fig. 1, a sudden fall of blood pressure can be seen at the end of an episode of desynchronized (REM) sleep and coincident with arousal of the rat.

Hypertensive rats

Blood pressure in the awake rats, 1 day after sino-aortic denervation, was very unstable (Fig. 3). Large oscillations, usually falls in pressure,

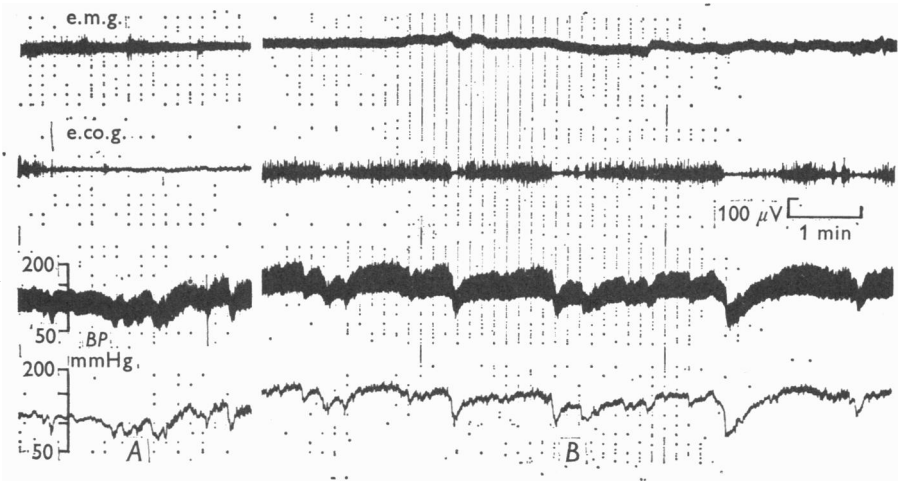

Fig. 3. Elevation of arterial pressure during synchronized sleep in a sino-aortically denervated rat (B). In the awake state (*A*) pressure oscillated markedly, with large drops when the animal moved or coincidental with discrete changes in body position. High blood pressure (180 mmHg) was observed during the synchronized sleep interrupted by large drops (40–80 mmHg) during electrocortical desynchronization coincidental with arousal.

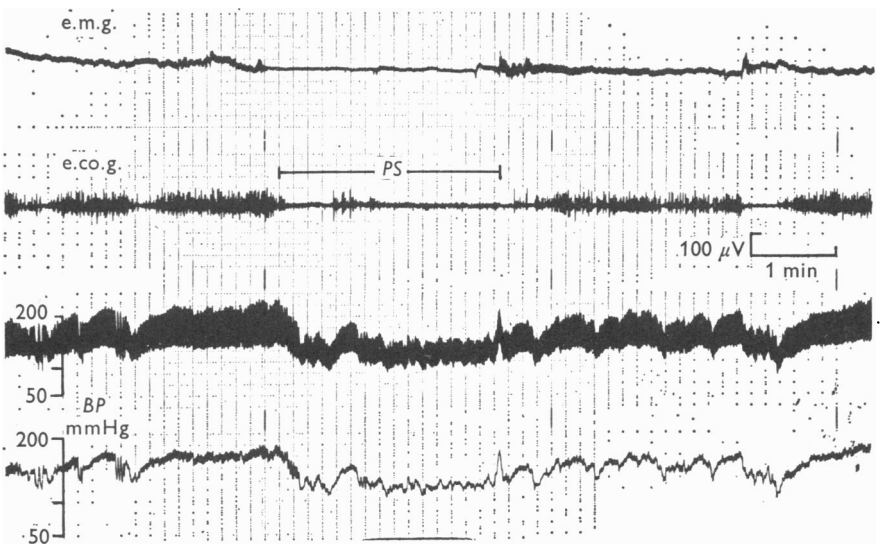

Fig. 4. Fall in pressure during desynchronized (REM, *PS* = paradoxical) sleep in a sino-aortically denervated rat. From a hypertensive level of 175 mmHg during the synchronized sleep the arterial pressure fell to 115 mmHg during the desynchronized (REM) sleep.

were observed when the animal moved or changed body position. In quiet wakefulness pressure was steadier, mean blood pressure of the nine rats studied being 135 ± 4 mmHg, a value significantly higher than that of the awake normotensive rats (114 ± 2 mmHg).

Synchronized sleep. Blood pressure typically increased from the waking value during synchronized sleep (Fig. 3). In 64% of the fifty episodes studied blood pressure rose by 14 ± 2 mmHg, in 16% it remained unchanged and in 20% a small drop (11 ± 2 mmHg) was observed. The direction

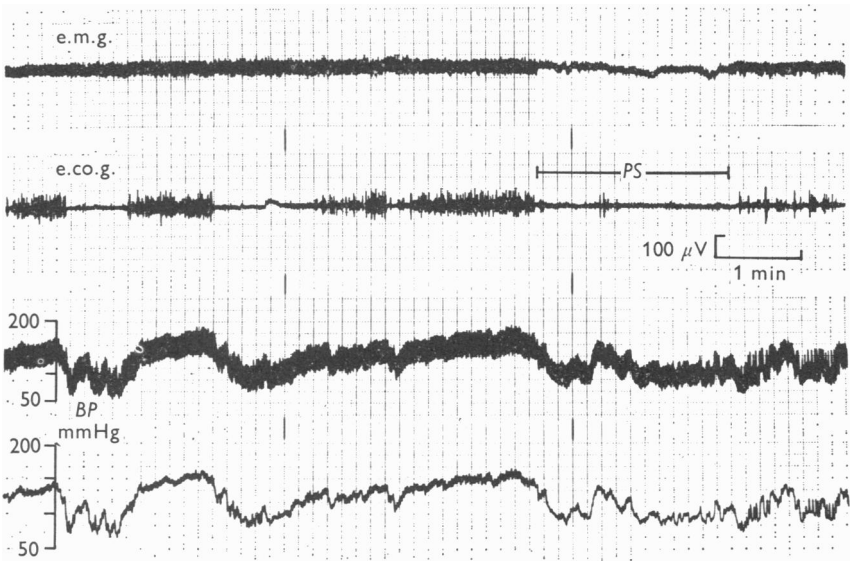

Fig. 5. Correlation between the electrocorticogram and arterial pressure in a rat with neurogenic hypertension. During desynchronization of the frontal electrocorticogram, e.co.g. (arousal or desynchronized sleep) the arterial pressure fell to a minimum and during synchronization (synchronized sleep) rose to a maximum.

of change during synchronized sleep did not depend on the value of blood pressure when the rats were awake. Considering all the fifty episodes studied the mean blood pressure exhibited a significant increase of 6·7 ± 1·7 mmHg. As in the control rats, the denervated animals presented fluctuations of blood pressure during the electrocortical desynchronization coincidental with arousal. However, these fluctuations were greater and usually consisted of a drop in pressure as large as 40–80 mmHg (Fig. 3).

Desynchronized (REM) sleep. Contrary to the discrete pressure rise seen in the normotensive rats during desynchronized (REM) sleep the animals with neurogenic hypertension showed a tendency to hypotension

(Figs. 2 and 4). From the total of forty-five episodes studied in nine rats, 82% exhibited a tonic decrease in pressure (7–53 mmHg with a mean of 29 ± 2 mmHg), 9% had no tonic changes and 9% presented a small tonic increase (4–22 mmHg with a mean of 10 ± 4 mmHg). The average change for all the forty-five episodes studied was a significant decrease of $23{\cdot}0 \pm 2{\cdot}6$ mmHg in mean arterial pressure. Since the pressure tended to rise in the control rats and to drop in the rats with neurogenic hypertension the level of the mean pressure in the denervated animals during desynchronized (REM) sleep was actually significantly lower than in the normotensives, respectively, 106 ± 2 mmHg and 121 ± 2 mmHg. As for the normotensive rats, the phasic alteration observed in sino-aortically denervated rats consisted of an increase in pressure. In Fig. 2, six episodes of paradoxical sleep obtained from the same rat are given, showing the tonic hypotensive alterations on which the phasic alterations are superimposed. The close correlation between pressure level and electrocortical activity throughout the wakefulness–sleep cycle was quite remarkable in the rats with neurogenic hypertension. As illustrated in Fig. 5, the lowest blood pressure levels concided with the electrocortical desynchronization of the desynchronized (REM) sleep or concidental with arousal and the highest hypertensive levels were attained during electrocortical synchronization.

DISCUSSION

In normotensive rats during synchronized sleep pressure was found to be steady and slightly lower than during the desynchronized (REM) sleep displaying approximately the same value as during arousal, while in those rats subjected to baroreceptor denervation the highest values of neurogenic hypertension were observed during synchronized sleep. The same phenomenon was described recently in denervated dogs (Ferrario *et al.* 1969). This is however at variance with earlier reports which indicated that sino-aortically denervated dogs exhibit a fall in pressure during sleep (Grimson, Kernodle & Hill, 1944; Heymans & Bouckaert, 1934; Samaan, 1934). Intact cats showed a mild reduction of arterial pressure during synchronized sleep but after the sino-aortic areas were denervated the fall became rather exaggerated (Guazzi & Zanchetti, 1965), even though during wakefulness, the denervated animals exhibited a moderate hypertension similar to that seen in the denervated rats. The mechanism responsible for the hypertension in dogs and rats in synchronized sleep in the absence of baroreceptor function is not clear. A depression of neural activity seems to occur in this period (Jouvet, 1967; Moruzzi, 1972) but the depression could be more pronounced in those areas that inhibited the sympathetic outflow, the baroreceptor activity

thus preventing the rise of blood pressure in the control rats. A possibility already considered (Ferrario *et al.* 1969) is that in the absence of baroreceptor activity there is a release of cortical inhibition and consequently an increase in the sympathetic tonus.

Contrary to what has been widely reported for the cat (Candia *et al.* 1962; Gassel *et al.* 1964; Guazzi & Zanchetti, 1965; Iwamura *et al.* 1968; Kanzow *et al.* 1962; Mancia *et al.* 1971), blood pressure in the rat shows an increase during desynchronized (REM) sleep. In this state of the wakefulness–sleep cycle blood pressure in the rat exhibits sharp oscillations, as during arousal. A marked reduction of the electrical activity of sympathetic nerves was described in the cat during desynchronized (REM) sleep (Baust, Weidinger & Kirchner, 1968; Iwamura, Uchino, Ozawa & Torii, 1966), which is consistent with the arterial pressure fall seen in this species with intact or denervated sino-aortic areas. In the rat, however, hypotension during desynchronized (REM) sleep only appears when the sino-aortic baroreceptor areas are denervated, whereas in the intact animals a rise in pressure is usually seen. This fact suggests that desynchronized (REM) sleep affects both the sympathetic outflow and the sensitivity of the baroreceptor reflex. The net result on the level of arterial pressure varies according to the animal species studied; in the rat, pressure usually rises and in the cat it drops. In man, there is evidence that the baroreceptor reflex sensitivity is increased (Bristow *et al.* 1969; Smyth *et al.* 1969) but the net result has been described as an increase (Khatri & Freis, 1967; Snyder *et al.* 1964) or as a decrease (Bristow *et al.* 1969; Smyth *et al.* 1969) in blood pressure. Chemoreceptors too play an important role in blood pressure regulation during desynchronized (REM) sleep in the cat by counteracting the exaggerated drop in pressure (Guazzi *et al.* 1968). The technique used for denervation of the aortic baroreceptor in the rat produces no damage to the vagus trunk (Krieger, 1964) and to those chemoreceptor fibres that ascend by that route (Krieger & Marseillan, 1963). The activity of those chemoreceptor fibres could prevent the blood pressure of the denervated rats from dropping to such a low level as in the cat, in which they are severed together with the baroreceptor fibres.

The comparative behaviour of blood pressure during the three states of the wakefulness–sleep cycle of the rat requires some comment. It seems that there is a tendency for blood pressure to behave somewhat similarly in desynchronized (REM) sleep and in arousal when its characteristics are compared with those observed during synchronized sleep, specially after denervation of the baroreceptors. Several authors have reported such parallelism for other physiological phenomena. Cortical irrigation, for instance, increases in the cat during both arousal provoked by sensory stimulation (Kanzow & Krause, 1962) and desynchronized (REM) sleep

(Kanzow *et al.* 1962; Coccagna *et al.* 1971). Cortical and subcortical impedance is reduced, as related to synchronized sleep, during desynchronized (REM) sleep and arousal (Birzis & Tachibana, 1964). The threshold to evoke movements by electrical stimulation of the motor cortex during the desynchronized (REM) sleep is also closer to that found in arousal than to the level found in synchronized sleep (Hodes & Suzuki, 1965). There is no satisfactory explanation for such a peculiar parallel but it indicates that a common mechanism may be involved in the parallel changes undergone by the physiological parameters mentioned above during wakefulness and deep sleep.

Dr Cesar Timo-Iaria collaborated with us in developing the method for recording the wakefulness sleep cycle in the rat.

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