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THE REGULATION OF PARADOXICAL SLEEP BY THE HYPOTHALAMO-HYPOPHYSIS

M. JOUVET

Département de Médecine Expérimentale, INSERM U 52, Faculté de Médecine, Université Claude Bernard, 8 Ave. Rockefeller, 69373 Lyon Cedex 2, France

INTRODUCTION

In his classical review (24) Moruzzi was confronted, in different chapters, with the problem of integrating the alternation of slow wave sleep (SWS) and paradoxical sleep (PS). Since, according to Moruzzi, the hypothalamus was responsible for the alternation of SWS (controlled by the anterior hypothalamus) and waking (controlled by the posterior hypothalamus), the decrease of SWS after rostral hypothalamic lesion was easily understood, but how could the brain stem mechanisms of PS be integrated with SWS? In order to explain the decrease of both SWS and PS which follows preoptic basal forebrain lesion, Moruzzi cited earlier explanations by McGinty and Sterman (22) and Sterman and Clemente (38) according to whom the basal forebrain lesion releases a process which inhibits the pontine structures that trigger PS. Then Moruzzi suggested that this process may be "in fact a release of the activating reticular system" (p. 79-119 in 24). Since 1972, numerous developments have been made in neuroanatomical tecniques and in lesioning methods (which permit only perikarya to be destroyed). In this paper written in the memory of my great friend, Giuseppe Moruzzi, I will summarize the results of some recent experiments undertaken to investigate both the discrepancies between the "serotonin" (5HT) and "rostral hypothalamic" SWS hypothesis and the nature of the facilitatory and inhibitory controls of PS from the hypothalamo-hypophysis.

THE HYPNOGENIC EFFECT OF 5HT: ITS HYPOTHALAMIC TARGET

The experimental evidence pointing to a relationship between serotonin (5HT) and sleep has been the subject of numerous reviews (12) (18). It was shown earlier (26) that 5HTP, when injected systemically, intraventricularly or intracisternally, could restore both deep slow wave sleep (SWS_2) and PS in an insomniac cat pretreated with P. chlorophenylalanine (PCPA) (an inhibitor of tryptophan hydroxylase) (17). Unfortunately, these methods do not demonstrate the target of the central effect of 5HTP. In order to solve this problem we injected a small amount of L-5HTP (5-10 µg dissolved in 0.5 µl of artificial CSF) in the brain stem of PCPA pretreated cat. The topography of the diffusion of intracerebral injected 5HTP was controlled either by adding ^{14}C-5HTP to the injected 5HTP with subse-

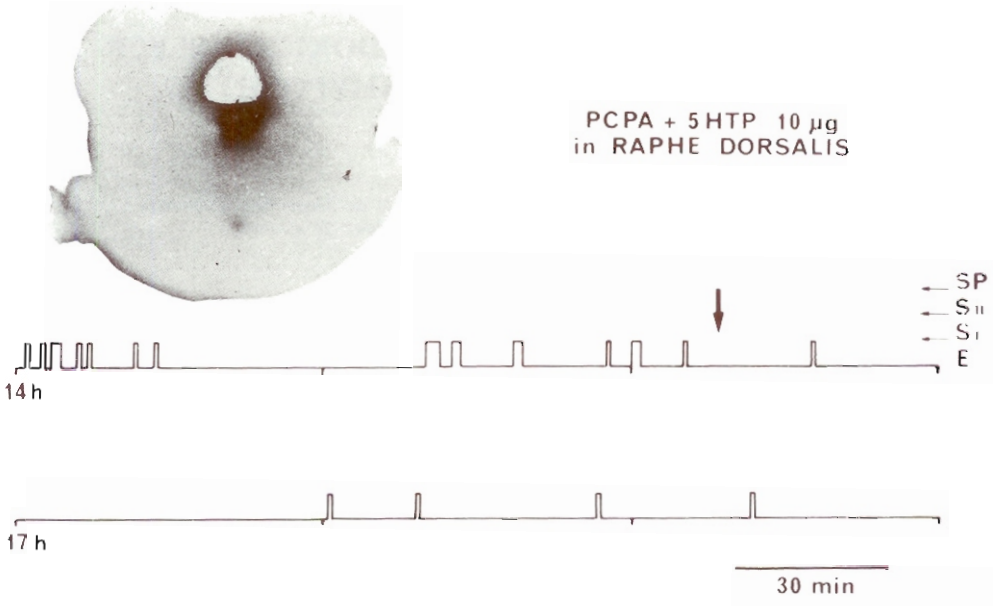

Fig. 1. — *L5HTP injection (10 µg, arrow) into the nucleus raphe dorsalis does not restore sleep in a PCPA pretreated cat.*

The localization of 5HTP injection is shown by autohistoradiography of a coinjected small amount of ^{14}C5HTP (1µl — 2,2 µCi). E: waking; S1; light SWS.

quent autohistoradiography or by using immunohistochemistry for 5HT immunoreactivity. At first, the results were negative (Fig. 1). Indeed, injections of 5HTP into the regions of the solitary tract, of the dorsal and ventral bulbo-pontine reticular formation, of the locus coeruleus, raphe nuclei and mesencephalic reticular formation did not suppress PCPA induced insomnia (31). Thereafter, bilateral injection of 2 µg of 5HTP were performed in the hypothalamus. As shown in Fig. 2, dramatic hypersomnia (with both SWS_2 and mainly PS) could be induced after a latency of about 60 min. These reversible hypersomnias were similar to the most intense hypnogenic effects obtained after systemic injection of 5 mg/kg of 5HTP. A comparison between the negative and positive injection sites demonstrated that the hypnogenic effects were obtained when 5HT immunoreactivity was located in the rostral and ventral part of the hypothalamus in the region of the paramedial preoptic area (8) (Fig. 3).

Thus, the only (or the main) hypnogenic target of 5HTP is the rostral hypothalamus which is strongly innervated by 5HT terminals originating from the rostral raphe (2). Of course, the PCPA-5HTP paradigm does not prove that only indolamines are necessary for induction of SWS. Indeed, besides its effects on 5HT biosynthesis, PCPA may alter other biochemical pathways, since it also inhibits the biosynthesis of adrenaline (5). But the fact that insomnia is also provoked

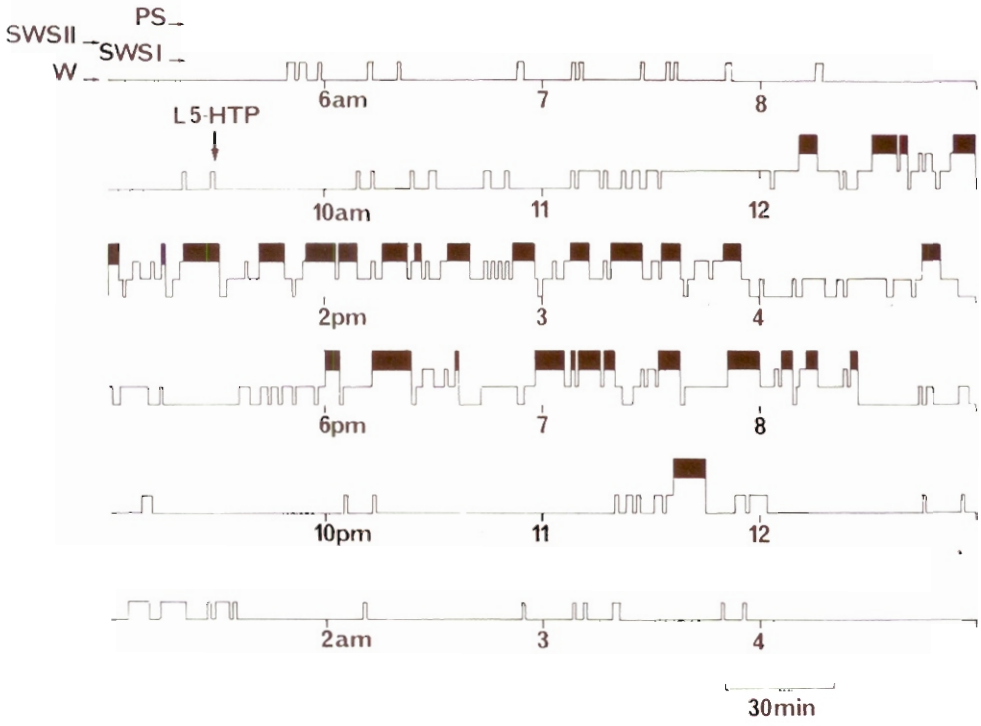

Fig. 2. — *L5HTP injection (4μg, arrow) bilaterally in the rostral hypothalamus (preoptic area) in an insomniac PCPA pretreated cat is followed after a 150 min delay by significant increase of PS which lasts during 9 hours.*

by the destruction of the raphe system (which destroys 5HT perikarya) (12) or by intraventricular injection of 5-7HT (9) (which depletes 5HT terminals) affords further evidence of a relationship between 5HT and SWS and "a contrario" suggests that it is the release of indolamines in the rostral hypothalamus that induces first SWS and secondarily PS. The mechanism of the hypnogenic effect of 5HTP (or 5HT) is still unknown. A direct post-synaptic effect is unlikely: firstly, there is no immediate suppression of PCPA induced PGO activity; secondly, there is a long interval between intrahypothalamic injections and the reappearance of SWS and PS (40-60 min). Conversely, when 5HTP is injected systemically, the PCPA induced PGO activity is almost immediately suppressed (1-2 min) (26). In such a case it is likely that the restoration of 5HT at 5HT terminals, located presynaptically on "PGO on" cells (28), is responsible for the inhibitory effect of PGO activity (27). After systemic injection of 5HTP, however, the latency for the restoration of both SWS and PS is similar to the intrahypothalamic injection (50-60 min). Such a lapse between local or systemic injection of 5HTP and the restoration of sleep suggests that 5HT may act as a local neurohormone and induce, directly or indirectly, the synthesis and/or the liberation of some factor(s) necessary for the chain of events inducing sleep. It is well known that the unitary activity of

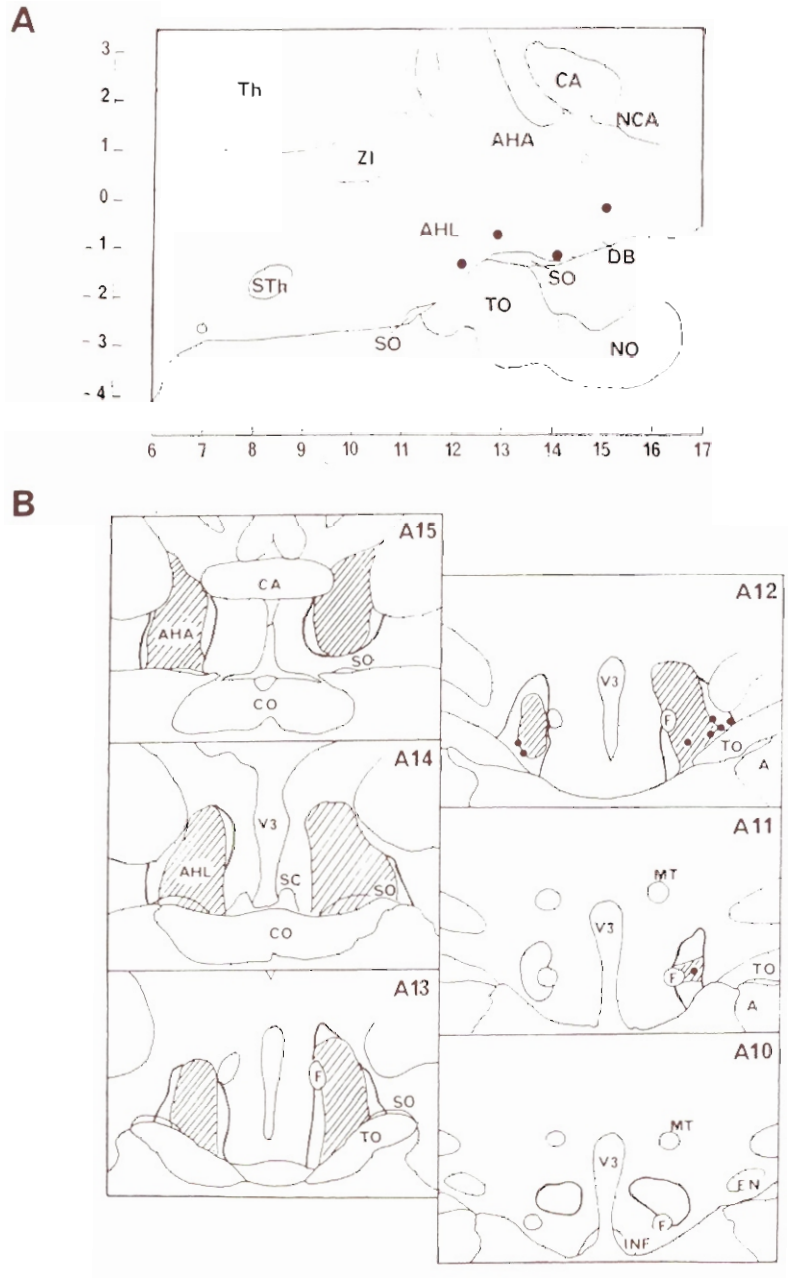

Fig. 3. — *Intrahypothalamic 5HTP injection sites.*

A: sagittal aspect of intrahypothalamic 5HTP injection sites. Black dots represent positive injection sites and open circles represent negative injection sites. Ordinate and abscissa indicate vertical and rostro caudal stereotaxic planes respectively. B: schematic drawing of frontal section illustrating the diffusion of transformed 5HT from injected 5HTP demonstrated by 5HT immunohistochemistry (Hatched area). In the area surrounded by thick lines, there were fine 5HT fibers. Dots indicate the 5HT immunoreative cells. From Denoyer *et al.* (8).

5HT perikarya is increased during waking and decreased during SWS (23), while the liberation of 5HIAA from 5HT terminals (as measured by voltammetry) is also increased during waking and decreased during SWS (3). These findings have been considered as a proof against the involvement of 5HT in sleep mechanisms (13, 23). However, the following hypothesis may explain these contradictions: 5HT may be liberated during waking in the RPO area and at the same time be responsible for the events which initiate SWS. In fact, there is, in the cat, a correlation between the duration of waking (increased by instrumental method) and the subsequent amount of SWS (42). Finally, whatever the mechanism of the sleep inducing effect of 5HTP might be, these results strongly suggest that the RPO plays a determinat role, not only in the restoration of SWS but also in the restoration of PS. For this reason, we undertook limited destruction of the rostral hypothalamus perikarya with ibotenic acid.

Paradoxical sleep suppression after anterior hypothalamic lesion

Ibotenic acid (IBO) is an excitatory amino-acid which selectively destroys most neuronal cell bodies while leaving the axons intact (19).

IBO was injected bilaterally (0.9-2 µl) at the following coordinates: A12-A15-L2,5-H-4,5, in 6 cats. This lesion was followed by a most dramatic and long lasting insomnia. PS and SWS_2 were completely suppressed for 6 to 17 days (Fig. 4). Three to 4 weeks after the lesion, the daily amounts of PS were still significantly decreased while SWS^2 was still totally absent in 2 cats (32).

During the first 2-5 days these insomniac cats developed a transient hyperthermia (39-41° C). Thereafter, the rectal temperature was normal (38.5° C) at room temperature. A totally insomniac cat was registered at different ambient temperatures (20-25-30° C) on the 9th day without any alteration of the total insomnia. The lesion common to each cat was strikingly similar to the hypnogenic area delimitated by 5HT-IR after intra-hypothalamic injection of 5HTP. It destroyed the cell bodies of the paramedial part of the preoptic area. It did not involve the paraventricular preoptic area, nor the paraventricular, supraoptic or suprachiasmatic nuclei. In two cats there was a small rostral extension of the lesion in the basal and medial portion of the diagonal band of Broca.

The most severe decreases in SWS_2 and PS following the rostral hypothalamus lesions are similar to those subsequent to a subtotal lesion of the raphe system (12). Thus, the medial preoptic area constitues a link between the long suspected role of 5HT in sleep mechanisms and the important role played by the anterior hypothalamus in the regulation of SWS_2 mechanism, "which would appear to be mostly a strategic post-synaptic ensemble of neurons where the 5HT terminals act to trigger or modulate the cerebral mechanisms synchronizing the cortical activity" (12). However, the suppression of PS in our cats was unexpected. It was more intense and immediate than in the series of cats subjected to electrolytic lesions of the preoptic area, lateral anterior hypothalamus and the diagonal band of Broca (22). According to Szymusiak and Satinoff (40), the decrease of PS

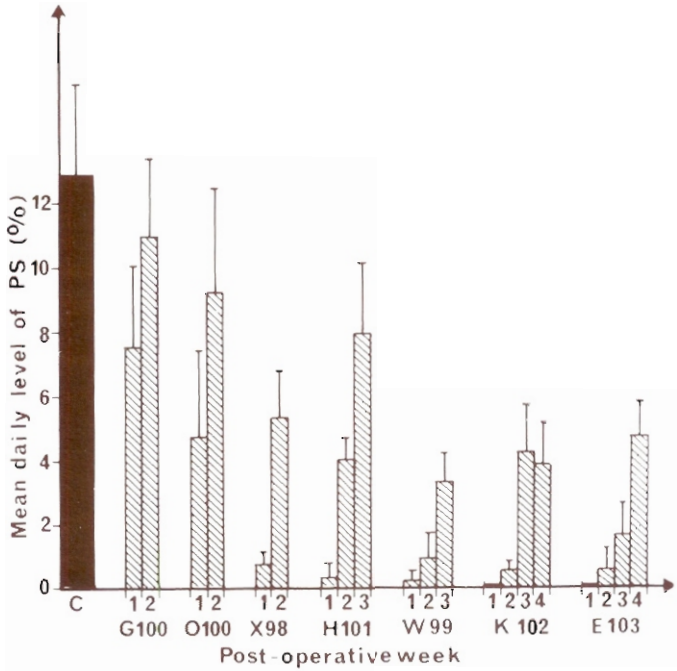

Fig. 4. — *Decrease of PS after lesion of the cell bodies of the preoptic area with ibotenic acid.*

PS amount is expressed as percentage of recording time (24 h/day) ± SEM during control (C) and during the 1, 2, 3 or 4th week after the lesion (1, 2, 3, 4) for 7 cats. From Sallanon *et al.* (32).

which is observed after electrolytic lesion of the rostral hypothalamus in rats might be the result of thermoregulatory disturbances since sleep occurred if the rats were registered at high ambient temperature. We did not however observe this phenomenon in the cat recorded at different ambient temperatures.

It is therefore unlikely that thermoregulatory disturbances represent an explanation of the total disappearance of PS in RPO lesioned cats. Such a suppression might be explained by the disappearance of a hypothetical "PS factor" synthesized and/or liberated from the RPO. However, this hypothesis does not hold since PS still persists for weeks in a pontile or mesencephalic preparation totally disconnected from the hypothalamus (11). Since a mesencephalic preparation is still connected with the reticular activating system, the putative structure which is released after RPO lesion and which would appear to inhibit PS should be located more rostrally. For this reason, the posterior hypothalamus which has been considered for a long time as playing a significant role in waking (24) was a good candidate.

The postero-ventro-lateral hypothalamus and waking

This area, which belongs to the posterior magnocellular hypothalamus has many interesting features. It contains APUD-like cells which are able to decarboxlate

5HTP in PCPA pretreated cat so that 5HT-like immunoreactive cells are easily stained in the postero-lateral hypothalamic area: ventro-medial neurons are located along the surface of the ventro-medial hypothalamus, at a more caudal level, the 5HT-IR magnocellular neurons are aggregated in and around the tubero-mamillay nucleus, the medial and the lateral mamillary nucleus (30) (Fig. 5). Subsequent immunohistochemical investigation in the cat disclosed that the totality of histamine (HA)-containing perikarya were located in the same area (20). Wheter APUD 5HT-IR neurons are coexistent with HA-containing neurons is not yet clear. Projections of both APUD neurons and HA neurons have been mapped out rostrally to the RPO, diagonal band of Broca, cerebral cortex, hippocampus, amygdala and medial thalamus while caudally projecting axons have been observed in the pons and medulla.

The following results suggest that this group of HA and/or APUD cells may play a role in waking mechanisms:

1) The recording of unitary activity of neurons located in ventro-postero-lateral hypothalamus disclosed type II neurons displaying a slow tonic firing during active waking (2.25 ± 0.29 imp./s) which was significantly reduced during quiet waking (1.44 ± 0.28 imp./s). A further reduction occurred during SWS_1 (spindles) (0.43 ± 0.16). During SWS_2 and during PS, all neurons became silent, while they resumed their activity at awakening or a few seconds before (41).

2) Neuropharmacological investigations in the cat have also demonstrated a waking action of HA-containing neurons. Indeed, local micro-injection of α-fluoromethyl histidine, an inhibitor of histidine decarboxylase, in the area of HA neurons decreased significantly waking while in situ injection of SKF 91 488 (Homodimaprite), in inhibitor of histamine N. methyltransferase, increased waking. A significant increase of waking was also noticed after injection of HA in the RPO (21).

In *summary* the postero-ventro-lateral hypothalamus contains the totality of HA neurons which may coexist with APUD-5HT-IR neurons. Local pharmacologically induced increase or decrease of HA activity increases or decreases waking. Whether or not the "waking on" type 2 neurons located in this area are HA neurons is not yet proven. But these data suggest that the a group of neurons located in the HVL area have a role in waking mechanisms.

The postero-ventral hypothalamus controls PS mechanisms but is not the "hypothalamic waking center"

The demonstration of the waking enhancing role of the HVL does not automatically suggest that this area may control (inhibit) PS mechanisms. Indeed, lesion of the rostral raphe which enhances waking and suppresses SWS_2 does not suppress PS which can still occur during waking, as in narcoleptic episodes (12). Moreover, it has been demonstrated earlier that coagulation of the posterior hypothalamus which decreases waking either does not impair or decreases PS (39). For this reason, the destruction of the HVL perikarya was realized by local microinjection of ibotenic acid. This was followed by a dramatic and transitory increase

of PS (up to 53% during 10 h) accompanied by hypothermia. Then there was a secondary decrease of PS followed by a restoration of normal or even increased level of PS (33) *while waking was not significantly decreased* (Fig. 5). Thus, it is likely that some system of perikarya located in the HVL may tonically control PS, since their inactivation is followed by a significant increase of PS. It should be pointed out, however, that ibotenic lesion also altered cold defence mechanisms since PS increase was accompanied by a significant hypothermia. Further, these results do not suggest that the area of the HVL is crucial for waking mechanisms since normal amounts of waking were observed after a few days. The concept of a posterior hypothalamic center was discussed by Moruzzi when reviewing the effect of transsection or coagulation of the post-hypothalamus (24). Our results demonstrate that such a center is not located in the area of the HVL. Certainly more experiments are required (by lesioning only cell bodies) located dorsally in the posterior hypothalamus in order to verify the existence of such a "center" by inducing a long lasting decrease of waking.

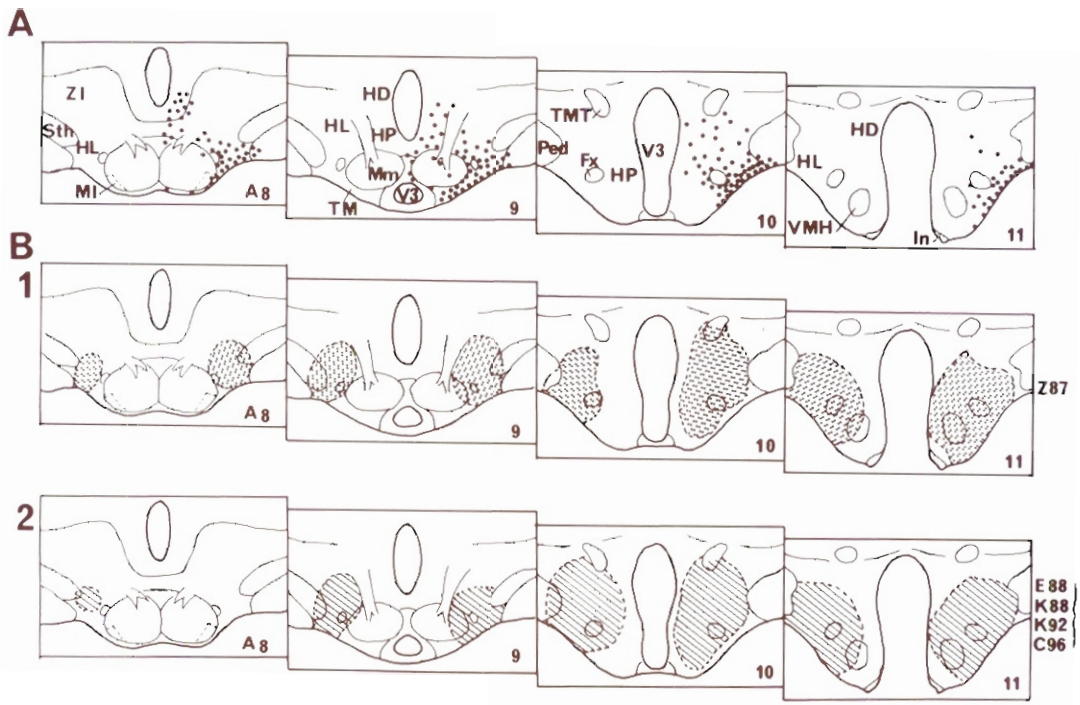

Fig. 5. — *Localization of serotonin immunoreactive hypothalamic neurons in the cat after 5-hydroxytryptophan administration (right side of the frontal section).*

Abbreviations: ZI, zona incerta; STh, nucleus subthalamicus; HL, area hypothalami posterior; Mm, nucleus medialis mamillaris; V3, third ventricule; TMT, fasciculus mamillothalamicus; Ped, pedunculus cerebri; Fx, fornix; VHM, area hypothalami medialis; In, infundibulum. B: schematic drawings of the bilateral cell body lesion, induced by ibotenic acid injection into the ventrolateral part of the posterior hypothalamus; 1: smallest lesion (cat Z87); 2: smallest common lesion for cats E88, K88, K92 and C96. From Sallanon *et al.* (33).

The RPO-HVL connection in PS control

There are numerous connections between the RPO and HVL which ascend or descend in the medial forebrain bundle (7, 36). These anatomical connections (whose immunohistochemical specificity is still unknown) provide a structural basis for possible inter-regulation between the HVL and the RPO area. In order to verify the hypothesis that the suppression of SWS_2 and PS after RPO lesion is consecutive to the enhanced activity of the HVL, we tried to inactivate reversibly the HVL by local injection of muscimol, an agonist of GABA. A receptors, (1) in cats whose RPO was previously destroyed by ibotenic acid. As shown in Fig. 6, an almost total suppression of both SWS_2 and PS was obtained in 2 cats during 2 weeks. Then in situ injection of muscimol (1-5 µg) was followed after a short latency (16-45 min) by an increase of both PS and SWS^2. At room temperature (23-24 ° C), this hypersomnia was accompanied by a great decrease of rectal

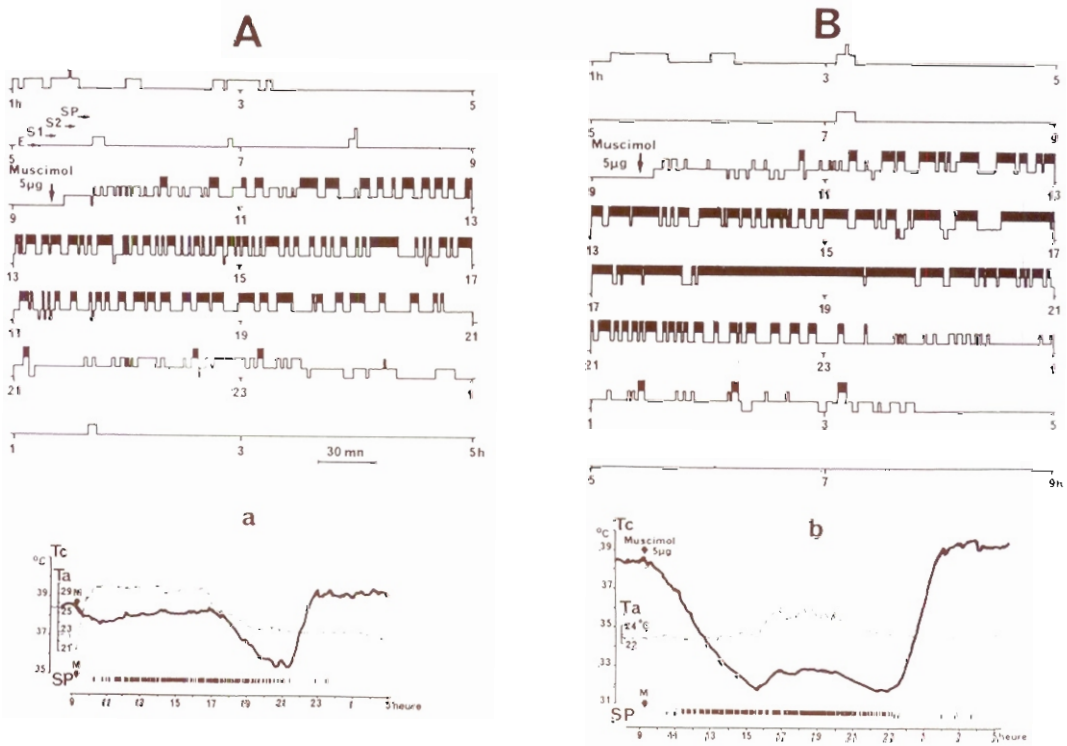

Fig. 6. — *Hypnogramm demonstrating the hypersomnia induced by a bilateral injection of muscimol (5µg/0.5 µl) in the ventrolateral part of the posterior hypothalamus during the 14th and the 16th post-operative day in an insomniac cat after destruction of the preoptic area.*

Under two experimental conditions. A: increased ambient temperature in order to maintain the central temperature close of preinjection level. B: stable ambient temperature 23° C ± 1. Abscissa: time in hours. Ordinates: waking (E), S_1 S_2 (SWS); PS: black area. a.b.: Effect of the muscimol injection on subcutaneous temperature (Tc) in these two experimental conditions. Abscissa: time in hours and PS epochs (black line). Ordinates: TC and ambient temperature (Ta). The arrow M indicates the muscimol injection. From Sallanon *et al.* (34).

temperature. However, a significant increase of both PS and SWS^2 still occurred even when the central temperature of the cat was kept normal (38° C) by increasing the temperature of the incubator. This hypersomnia which lasted 15 ± 2 h was followed in each case by the return of insomnia (34). These results lead to 2 main conclusion:

1) The RPO is not necessary for SWS_2 since an increase of SWS^2 may follow the inactivation of the HVL after RPO destruction. Thus, the "executive structure" responsible for SWS_2 should be located outside the RPO area.

2) The suppression of PS which follows RPO lesion is probably provoked by the increase of activity of some group of neurons located in the HVL. It is unlikely that the increase of PS was due to hypothermia since we could observe an increase of PS and SWS_2 at normal central temperature. However, a larger increase of PS was observed during hypothermia. This suggests that there may be some interaction between central thermoregulatory mechanisms and PS. In any case, the inhibitory control of the HVL area upon PS occurs in the lower brain stem.

Indeed, according to many experimental data, the "executive" structures responsible for the main characteristics of PS are located in the pons medulla (see reviews in 29, 37). There are several pontobulbar subsystems, cholinoceptive and/or cholinergic, responsible for muscular atonia, PGO activity and cortical activation. These neurons, which are selectively activated during PS ("PS on" cells) are thought to be tonically inhibited by "gating" or inhibitory systems ("PS off" neurons). The locus coeruleus and the raphe system are considered to be the main inhibitory systems. Whether "executive" cholinergic cells inhibit monoamine cells or conversely is not known but whatever the model of their interaction might be there is general agreement that PS "gating" and "executive" mechanisms are located in the pons-medulla.

Since the HVL area is complex and contains numerous coexistent or separate populations of several transmitters (HA) and peptides which project into the pontobulbar area, much work is needed in order to understand how HVL perikarya can inhibit for such a long time (weeks) PS mechanism probably by either facilitating the gating monoaminergic mechanism and/or inhibiting executive cholinergic systems.

However, besides this reciprocal interconnection between the RPO and the HVL in the control of PS other mechanisms involving both the hypophysis and the arcuate nucleus may also enhance PS.

The hypophyseal regulation of PS

The periodical and regular occurrence of PS in a pontile preparation without hypothalamo-hypophysis (and without substitutive therapy) for about 100 h proves that the essential mechanism responsible for both PS and its periodical appearance does not necessitate any hypothalamic or hypophyseal influences (11).

However, if an isolated hypophysis is left intact in the sella, after removal of the entire brain rostral to the pons, *including the arcuate nucleus*, there is

an increase of PS (up to 300 min/24 h) which is most significant when compared to the mean of 80 min/24 h recorded in the pontile preparation (14).

It is likely that the PS enhancing factor(s) are liberated from the pars intermedia since injection of extracts from the neuro-intermediate lobe may also increase PS in pontile cats(14). Thus, pituitary factor(s) may increase PS up to a level which is only observed during the rebound of PS which follows PS instrumental suppression in the normal cat. The mechanism of this PS facilitating effect is still unknown inasmuch as total hypophysectomy in the normal cat does not alter the sleep-waking cycle, nor suppress the rebound of PS which follows a 24 h instrumental suppression (35).

Since PS rebound does not occur in the pontile or mesencephalic cat (after instrumental suppression (11), it is probably caused by supramesencephalic mechanisms. The following experiments, performed in rats, suggest that increase of PS may be obtained both through pituitary factors and/or through neuronal influences originating from the arcuate nucleus.

Regulation of PS by the arcuate nucleus

Systemic injections of monosodium glutamate immediately after birth destroy the perikarya located outside the blood brain barrier, mostly in the arcuate nucleus (25). Thus, the pro-opio-melanocortine (POMC) containing perikarya are almost totally destroyed and the arcuate brain stem POMC pathways are severely altered as hown by the considerable decrease of ACTH, α-MSH, β-endorphin in the brain stem (16). After such lesions, however, the pituitary ACTH and POMC systems are still functional. However, if MSG pretreated rats are hypophysectomized, there occurs a significant decrease of POMC peptides of neuronal (arcuate nucleus) and hormonal (pituitary) origins (46).

Control untreated female rats and rats, pretreated after birth with 10 injections of MSG (4 mg/g), were hypophysectomized (Hypo) at 45-50 days and their sleep waking cycle continuously registered. As shown in Fig. 7, PS was not significantly impaired in MSG-Hypox rats while there was a small (35%) significant decrease of PS in normal Hypox rat. However, after 24 h of PS deprivation (with the so-called "swimming pool" technique) there was a normal immediate rebound in the control Hypox rats and in MSG rats while there was no rebound in Hypox-MSG rats (45). From these results the following conclusions may be drawn:

1) It is evident that neither the arcuate nucleus nor the hypophysis are necessary for normal amounts of PS in control conditions. However, the rebound of PS observed in MSG rats and the absence of rebound in MSG-Hypo rats demonstrate that the increase of PS during the rebound is mediated by PS facilitatory factors originating from either the arcuate nucleus or the hypophysis.

2) Thus, it is likely that the increase of PS during the rebound may be obtained through 2 complementary systems (each of them being sufficient): the first one is central and depends upon the neuronal system originating from the arcuate nucleus, while the second one is hormonal and is mediated by the hypophysis. Thus,

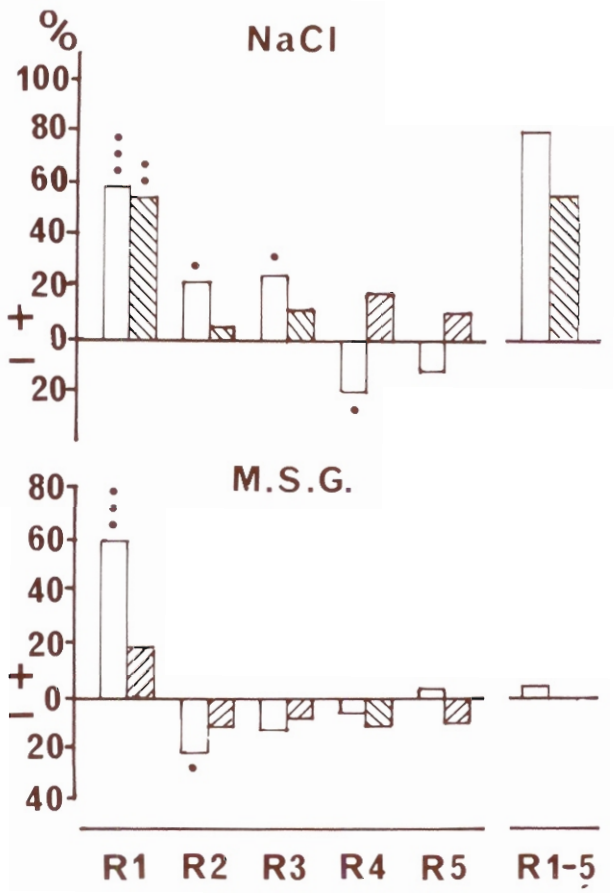

Fig. 7. — *Recovery of PS (rebound) (R) as expressed in percentage of PS* ($R = \frac{DR-DC}{DC}$).

DC is PS duration during control, DR is PS duration during recovery day 1 — 5 (R1 — R5). NaCl: control rats treated with NaCl after birth (white bar). Hatched area, control rat hypox. M.S.G.: rats pretreated after birth with monosodium glutamate. White bars, non hypox. Hatched area, Hypox. ... $P < 0.01$; .. $P < 0.05$; . $P < 0.02$ with control recording. Note that immediate rebound is possible in MSG treated rat, but that secondary rebond is impaired.

in the first case, it is probable that PS enhancing effects might be due to peptides processed centrally form POMC perikarya located in the arcuate nucleus since intraventricular injections of desacetyl-α MSH or corticotrophin-like intermediary peptide (CLIP) increase PS in the rat (4). In the second case, peptides from the POMC family (or from other known or unknown sources from the pituitary) may also facilitate PS in MSG treated non-Hypox rats through a blood borne (hormonal) mechanism (as is the case in the pontile cat with isolated hypophysis).

The problem of PS rebound

Since the discovery of PS, the phenomenon of "PS rebound" which follows instrumental PS suppression has been a riddle for sleep research. PS rebound

has been explained by different theories. Either an "hydraulic theory": a PS specific factor would "accumulate" in the brain or the CSF (or the blood) and then be "used up" during the compensatory rebound (see 12, 24). According to another hypothesis, PS rebound could be the consequence of the hypersensitivity of the receptors involved in PS mechanism (monoamines — acetylcholine) (43, 44, 47). The "stress" which is inevitably involved during PS suppression has been implicated in the behavioral alterations (hyperemotionality — analgesia, etc) which follow PS deprivation. However, the occurrence of PS rebound in Hypox rats cannot be explained by the involvment of the classical pituitary-adrenal hormonal system involved in stress.

Our results do not support the first two theories of sleep rebound. The hypothesis of the accumulation of a specific PS factor is now untenable since MSG-Hypox rats *which have normal amounts of PS in control conditions* do not present any rebound. The supersensitivity hypothesis is also unlikely although it is not directly negated by our results.

The most probable hypothesis is that during the "stress" which occurs during PS deprivation, there is activation of both central (arcuate) and peripheral (pituitary) mechanisms. The occurrence of PS rebound in control Hypox rat (or cat) demonstrates that the peripheral and hormonal indices of stress (increase of the weight of adrenals, of ACTH or corticosterone) may be absent. In such a case, the dosage of putative POMC derived peptides (or other) in the brain and/or the CSF might indicate the involvment of the arcuate-brain stem system. How and where these factors originating from the arcuate nucleus may facilitate PS is unknown. A possible mechanism of action could be a direct or indirect inhibitory effect upon the activity of the monoaminergic neurons which gate the PS mechanism.

In any case, the MSG-Hypox rats appear as a suitable preparation to study both the central and peripheral factors involved in PS facilitation.

CONCLUSIONS

In the first part of this paper, we reviewed some evidence for a dual facilitatory (RPO) — inhibitory (HVL) control of PS, while the second part deals with the existence of a dual (arcuate — pituitary) facilitatory control of PS. Both systems may well work independently, but a possible unitary mechanism is possible.

There are, one the one hand, numerous data concerning the control both by 5HT (10, 15) and/or by the RPO (6, 7) of the arcuate nucleus. On the other hand, however, the data concerning the putative inhibitory effect of the HVL upon the arcuate nucleus and/or the pituitary are still scarce.

If the RPO-HVL control of PS involves both the arcuate and/or the hypophysis, then the deafferentation of the arcuate from both the RPO and HVL should lead to the restoration of sleep in an insomniac RPO lesioned cat.

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