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CHAPTER II

BRAIN SEROTONERGIC AND CATECHOLAMINERGIC SYSTEM: FACTS AND HYPOTHESIS

By WOJCIECH KOSTOWSKI

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A. INTRODUCTION

Recently, the relationship between monoaminergic (MA) neurons in the brain has become of increasing interest. Numerous findings of interconnections between catecholaminergic and serotonergic neurons provide important supporting evidence for interactions, in MA systems. The knowledge of these interactions opens new possibilities for explanation of such higher brain functions as reward and punishment mechanisms, emotion behavior and the sleep-wakefulness cycle. These functions may be regulated by reciprocal mechanisms including the parallel antagonistic neuronal systems—serotonergic and catecholaminergic (noradrenergic and dopaminergic). Such an organizaional model is compatible with the original theory of Brodie and Shore (1957) of a serotonin (5HT)-mediated tropotrophic antagonism of a cate holamine-mediated ergotrophic system.

B. ANATOMICAL ORGANIZATION AND INTERCONNECTIONS IN MA BRAIN SYSTEMS

The anatomical organization of MA-containing neurons have been mapped with the aid of histofluorescence methods combined with the use of stereotaxic lesions of discrete brain areas (Anden *et al.*, 1965, 1966). Most of the 5-HT cell bodies are located in the raphé area. These cells send both ascending and descending projections. The nuclei raphé pallidus, obscurus, and magnus provide projections to the spinal cord; the nuclei raphé obscurus and pontis project to the cerebellum (Bloom *et al.*, 1971, 1973; Olson and Fuxe, 1971). Most ascending 5-HT fibers arise from the anterior group of raphé nuclei (nuclei raphé medianus, dorsalis, intermedius, linearis, and nucleus centralis superior of Bechterew. 5-HT fibers terminate throughout wide regions of telencephalon and diencephalon (Briggs and Kaelber, 1971' Fuxe *et al.*, 1970; Morgane and Stern, 1972). Projection systems of the anterior raphé group are of particular importance since many of these lie within the limbic midbrain area and comprise the limbic forebrain structures such as the hippocampus, septum, and amygdaloid complex. It is assumed that these limbic structures are reciprocally connected with the raphé system. The neural systems of the midbrain and forebrain limbic areas are extensively involved in sleep–waking mechanisms (Naute *et al.*, 1966). Projections from the anterior portions of the raphé complex as well as other brainstem structures ascend via the medial forebrain bundle containing various MA fibers. According to Morgane and Stern (1973a) raphé nuclei form three groups—anterior, middle, and posterior. The middle and posterior groups project (not via the medial forebrain bundle) to structures other than those to which the anterior project. Lesions of

the middle and posterior raphé nuclei do not affect 5-HT forebrain concentration (Morgane and Stern, 1973a). On the other hand, lesions of the anterior group cause decrements in forebrain 5-HT level in cats and rats (Jouvet *et al.*, 1966; Renault, 1967; Rosecrans and Sheard, 1967; Kostowski *et al.*, 1968; Giacalone and Kostowski, 1969) and cause only a slight decrease in 5-HT concentration in the spinal cord (Giacalone and Kostowski, 1969). Stimulation of the midbrain raphé leads to a release of forebrain 5-HT in rats (Aghajanian *et al.*, 1967; Kostowski and Giacalone, 1969; Kostowski *et al.*, 1969). Björklund *et al.* (1971) have described a new fluorescing system containing an unknown intraneuronal monoamine (probably an indoleamine). Cell bodies of this system are located within the nuclei raphé medialis and linearis caudalis. Their axons ascend, probably via the medial forebrain bundle, to the prosencephalon.

The ascending noradrenergic system forms two main bundles—dorsal and ventral. The dorsal bundle originates in the dorsolateral portion of the locus coeruleus (LC) and projects to both the paleocortical and neocortical areas. The ventral pathway projects from cells located in the pons and medulla beyond the LC and innervates the hypothalamus, basal forebrain region, and the amygdaloid complex (Jones, 1969; Fuxe *et al.*, 1970; Olson and Fuxe, 1971a, b; Ungerstedt, 1971; Jalowiec *et al.*, 1973). Maeda and Shimizu (1972) described the so-called "intermediate" noradrenergic (NA) system originating in the A-5 cell group and locus subcoeruleus as well as in the anterior LC area; this system innervates periventricular hypothalamic area.

Recently 2,4,5-trihydroxyphenylalanine (6-OH-dopa) has been introduced as a tool in the mapping of central NA pathways (Jacobowitz and Kostrzewa, 1971; Sachs and Jonsson, 1972; Sachs *et al.*, 1973). 6-OH-dopa causes intense fluorescence in NA fibers and produces degeneration of a large number of the central NA terminals (Malmfors and Thoenen, 1971). Using this method Sachs *et al.* (1973) demonstrated that NA fibers from the LC could be traced into the cerebellar and telencephalic cortices, the geniculate bodies, thalamus, rhombencephalon, and lateral hypothalamus. It is noteworthy that the ventral NA pathway is not markedly affected by 6-OH-dopamine.

It is possible that the LC and raphé are anatomically connected. Olson and Fuxe (1971) demonstrated a fiber projection to the raphé originating from the medial and ventral portions of the LC. Projections from the LC to the raphé form a partially crossed system responsible for the cortical innervation and innervation of raphé, hypothalamus, and vagal area. According to Loizou (1969) bilateral lesions of the LC cause disappearance of NA nerve terminals in the raphé area. Projections from the raphé to the LC have not been, however, definitively established. Brodal *et al.* (1960) have found that some neurons of

the raphé nuclei have axons which bifurcate—one branch ascends anteriorly and other descends posteriorly. Some authors have postulated polysynaptic connections between the raphé and LC (Routtenberg, 1973).

Most of the dopamine (DA)-containing cell bodies are located within the substantia nigra (SN) and in an area dorsal to the nucleus interpeduncularis. The DA nerve terminals are located mainly in the neostriatum (nucl. caudatus and putamen), tuberculum olfactorium, nucl. accumbens, median eminence, nucl. paraventricularis, and the amygdaloid complex (Carlsson *et al.*, 1962; Dahlstrom and Fuxe, 1964; Fuxe, 1965). DA-containing cells form the nigrostriatal tract with axon terminations within the striatum (Anden *et al.*, 1964, 1965, 1966; Poirier and Sourkes, 1965; Sourkes and Poirier, 1965). Mc Lennan (1965) confirmed the dopaminergic nature of the nigrostriatal tract demonstrating that electrical stimulation of the SN results in the release of DA in the ipsilateral neostriatum. Another DA system is formed by cells belonging to the A-10 group, projecting to limbic structures (so-called dopaminergic mesolimbic system) such as the tub. olfactorium, nucl. accumbens, nucl. amygdaloideus centralis, and nucl. interstitialis stria terminalis (see Hornykiewicz, 1972). Some DA cell bodies send their axons toward the caudal part of the raphé system (nuclei raphé pallidus, magnus, and obscurus). On the other hand numerous 5-HT terminals have been found in the SN using an electromicroscopic technique (Parizek *et al.*, 1971).

In summary, the anatomical data provide evidence for the existence of functional interactions between monoaminergic brain systems. Such interactions appear to play a fundamental role in mechanisms of the sleep–waking cycle and in orther important functions of the brain.

1. Interactions Between Brain 5-HT and DA Systems

It is possible that 5-HT and DA act reciprocally within the striatum, the area receiving both 5-HT and DA nerve terminals from the raphé and SN, respectively. Pharmacologically induced increases in striatal DA level is accompanied by decreased 5-HT concentration in this area (Hassler and Bak, 1966; Parizek *et al.*, 1971). L-Dopa, the precursor of DA, when given in large doses produced substantial decrease in brain 5-HT in mice (Everett and Borherding, 1970), probably due to release and/or displacement of 5-HT by DA synthesized from dopa in 5-HT storage sites. Fuxe *et al.* (1971) reported that there is a possibility of conversion of dopa to DA in 5-HT nerve terminals that contain aromatic amino acid decarboxylase. On the other hand it was found that large doses of 5-HTP, the precursor of 5-HT, decreases the DA content in the striatum, probably due to displacement of DA by newly formed 5-HT in DA-nerve terminals (Goldstein *et al.*, 1969; Ng *et al.*, 1972a,b). Using

^{3}H-DA, Ng *et al.* (1972b) provided direct evidence that 5-HTP may release DA from DA terminals in the striatum. This effect appears due to the conversion of 5-HTP to 5-HT, since it was inhibited after treatment with d-10 (methyl-dopa-hydrazine (MK-485), an inhibitor of l-amino acid decarboxylase. Thus, mutual displacements in the storage sites between 5-HT and DA might be assumed. Drugs which stimulate DA nerve terminals and act upon DA receptors such as amphetamines and apomorphine (Ernst and Smelik, 1966; Weissman *et al.*, 1966; Ernst, 1967; Fog *et al.*, 1971; Hornykiewicz, 1972) seem to influence the metabolism of 5-HT. Amphetamine does not consistently alter the level of 5-HT of the whole brain. (Laverty and Sharman, 1965; Pletscher *et al.*, 1964,1965) but does increase the concentration of this amine in some areas such as the pons and striatum (Beauvalett *et al.*, 1970). Amphetamine has also been reported to increase the turnover rate of 5-HT (Reid, 1967). It is noteworthy that apomorphine, a drug known to directly (and indirectly) stimulate DA receptors (Anden *et al.*, 1967; Ernst, 1967, 1969; Ungerstedt, 1971; Costall and Naylor, 1973) increases the turnover of 5-HT and increases the brainstem concentration of this amine in rats (Grabowska and Michaluk, 1974). Antagonists of 5-HT such as BOL-48, methysergide, and lysergic acid diethylamide (LSD-25) as well as the 5-HT depletor p-chlorophenylalanine *(pCPA)* prevent amphetamine-induced rearing in mice (Lapin *et al.*, 1972). pCPA administered to young chicks antagonizes the postural changes elicted by amphetamine (Schrold and Squiers, 1971). On the other hand pCPA increases motor excitation induced by amphetamine, apomorphine, and L-dopa in rats (Neil *et al.*, 1972). Motor hyperactivity as well as stereotyped behavior induced by amphetamine in rats is enhanced after lesions of the midbrain raphé area (Neil *et al.*, 1972; Kostowski *et al.*, 1972; Gumulka *et al.*, 1973). Since stereotypic movements are phenomena involving stimulation of striatal DA receptors (Van Rossum, 1970; Costall *et al.*, 1972), the data described above may suggest that lesions of the raphé system leads to increased reactivity of striatal donaminergic mechanisms. Drugs which block dopamine receptors, such as the neuroleptics, have also been reported to affect the brain 5-HT system. The release of 5-HT induced by both reserpine and electrical stimulation of the raphé nuclei is markedly reduced by chlorpromazine (CPZ) (Gey and Pletscher, 1961, 1965; Kostowski and Giacalone, 1969a). The increase in forebrain 5-hydroxyindoleacetic acid (5-HIAA) level due to electrical stimulation of the hippocampus may be also blocked by CPZ (Kostowski and Giacalone, 1969; Giacalone and Kostowski, 1968; Gumulka *et al.*, 1970). CPZ is assumed to affect the release of 5-HT, decrease its storage (Gey and Pletscher, 1965), and increase its turnover (Borzecki *et al.*, 1970). We have recently reported (Kostowski *et al.*, 1972); Gumulka *et al.*, 1973) that an intact

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serotonergic system is necessary for the cataleptogenic activity of neuroleptics since lesions of the midbrain raphé led to a marked reduction of the effects of both CPZ and haloperidol (see Table I). It is noteworthy that pCPA as well as LSD-25 cause similar effects. Since catalepsy due to neuroleptics is at least partly related to a blockade of DA receptors within the striatum one may assume that raphé lesions exert profound effects upon the function of the DA nigrostriatal pathways. These data support the hypothesis of an interaction between 5-HT and DA systems in the brain. The general conclusion should be that destruction of the 5-HT system leads to increased activity of DA nigrostriatal pathways (Kostowski *et al.*, 1972). Further experiments, however are needed to confirm this hypothesis and to clarify the details of this interaction. There is also some indirect evidence that the DA system may influence the activity of the raphé. The microinjection of DA to the pontine raphé area causes intense cortical synchronization in cats (Kostowski and Gumulka, 1974c; see Fig. 1). It was also observed that this effect of DA was partially or completely blocked by haloperidol (Kostowski and Gumulka, 1974c).

Stimulation and lesions of the 5-HT system of the raphé and DA nigrostriatal pathways elicit opposite behavioral effects. The destruction of the raphé in cats decreases the percentage of slow-wave sleep (SWS) and causes a state of permanent behavioral and EEG arousal during the first 3–4 days (Renault, 1967, Jouvet, 1972, 1973). Striking insomnia and a state of agitation as well as cortical EEG arousal is also seen in rats after coagulation of anterior raphé nuclei. The intensity of motor agitation is significantly correlated with the decrease in both forebrain 5-HT and 5-HIAA. (Kostowski *et al.* 1968). Parachloromethamphetamine, a drug which provides for depletion of brain 5-HT (Fuller *et al.*, 1965; Fuller and Hines, 1970), induced marked EEG arousal (Delorme *et al.*, 1966). Parachlorophenylalanine is known to induce almost total insomnia due to a reduction in both stages of sleep—SWS and paradoxical sleep (PS) in cats (Delorme *et al.*, 1966; Mouret *et al.*, 1967; Pujol *et al.*, 1971; Cohen *et al.*, 1970). Similar effects were observed in rats, rabbits, monkeys, and man (Mouret *et al.*, 1968; Florio *et al.*, 1968; Weitzman *et al.*, 1968; Sehard, 1969; Wyatt *et al.*, 1969; Sjoerdsma *et al.*, 1970). It was also found that there was a significant correlation in the rat between decreased SWS and the decrease of cerebral 5-HT (Mouret *et al.*, 1968). However, these results have not been confirmed by some authors (Rechtschaffen *et al.*, 1969). Other conflicting results have been obtained in cats and man (Cohen *et al.*, 1970; Wyatt *et al;* 1969, 1970). Damage of the nigrostriatal system in the cat produces an effect opposite to that resulting from damage of the raphé system. Stereotaxic coagulation of DA-cell bodies leads to akinesia, an inability to initiate motor activity, and in some cats provides for a permanent comatose

Table I

(Kostowski, W., Gumuka, W., and Czonkowski, A. *Brain Res. 48:* 443-446)

Experimental groups	No. of animals		Intensity of catalepsy (scored) ± S.E. at intervals after infection of drug		
			30 min	60 min	180 min
(1) Sham lesion	A	10	6.9 ± 1.5	10.0 ± 0.9	10.8 ± 0.7
	B	5	10.4 ± 1.0	11.0 ± 0.4	9.4 ± 1.0
(2) VR lesion	A	5	0.6 ± 0.6§	0.8 ± 0.8§	7.2 ± 2.2
	B	5	2.5 ± 1.2§	2.0 ± 0.8§	2.5 ± 0.8§
(3) DR lesion	A	8	0.4 ± 0.3§	0.5 ± 0.3§	1.5 ± 1.2§
	B	5	1.0 ± 0.8§	0.8 ± 0.8§	1.0 ± 0.8§
(4) LM lesion	A	6	4.1 ± 2.2	6.2 ± 1.5	10.3 ± 0.7
	B	5	8.4 ± 1.9	7.4 ± 1.9	8.6 ± 1.5
(5) Intact, saline	A	8	8.1 ± 1.3	9.4 ± 1.7	10.5 ± 1.4
	B	8	9.3 ± 0.8	9.6 ± 0.5	8.7 ± 0.8
(6) Intact, p-CPA	A	8	1.2 ± 0.7§§	2.8 ± 1.0§§	4.1 ± 0.4§§
	B	8	0.8 ± 0.4§§	1.6 ± 0.5§§	3.7 ± 1.2§§

*para-Chlorophenylalanine methylester (Pfizer).
**Fenactil (POLFA), 5 mg/kg s.c.
***Haloperidol (Janssen), 0.2 mg/kg s.c.
§p < 0.01 with respect to sham lesioned animals.
§§p < 0.01 with respect to saline (Student's *t*-test). VR, ventral raphe; DR, dorsal raphe; LM, lateral midbrain.

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	B	8	9.3 ± 0.8	9.6 ± 0.5	8.7 ± 0.8
(6) Int[illegible]t, p-CPA	A	8	1.2 ± 0.7[illegible]	2.8 ± 1.0§§	4.1 ± 0.4§§
	B	8	0.8 ± 0.4	1.6 ± 0.5§§	3.7 ± 1.2§§

*para-Chlorophenylalanine methylester (Pfizer).
**Fenactil (POLFA), 5 mg/kg s.c.
***Haloperidol (Janssen), 0.2 mg/kg s.c.
§p < 0.01 with respect to sham lesioned animals.
§§p < 0.01 with respect to saline (Student's t-test). VR, ventral raphe; DR, dorsal raphe; LM, lateral midbrain.

state (Jones, 1969; Jones *et al.*, 1969). It is of particular interest that a generally normal EEG pattern and EEG arousal have been observed in these animals (Jones *et al.*, 1969). In rats, however, no consistent data have been obtained—some authors have reported a decrease in motor activity following lesions of SN (Gumulka *et al.*, 1970d, while other have observed increased motor activity (Simpson and Iversen, 1971). It appears possible that, at least in cats, the DA nigrostriatal system plays a role in the maintenance of waking behavior and behavioral alertness but does not substantially affect the electrical activity of the cortex (Jouvet, 1972).

According to Jouvet (1967, 1969, 1972, 1973) the serotonergic system of the raphé is responsible for the induction of SWS and for cortical synchronization. Stimulation of the raphé in rats induces inhibition of motor activity, somnolence, and cortical synchronization (Kostowski *et al.*, 1969). In cats, stimulation of the raphé at low frequencies (2/second) induces cortical synchronization. This effect is enchanced by pretreatment with 5-HTP and blocked after LSD-25 (Kostowski, 1971). The physiological role of the raphé seems, to be however, more complex since EEG and vegetative and behavioral symptoms of arousal were obtained by stimulation (with a frequency of 6/second) of the pontobulbar raphé in rabbits (Polc and Monnier, 1970).

2. Some Biochemical and Behavioral Evidence for 5-HT and NA Interactions

The depletion of brain NA as a result of the inhibition of the conversion of DA to norepinephrine by inhibition of dopamine β-hydroxylase with U-14-624 (1-phenyl-3-/thiazolyl/-2-thiourea) was accompanied by an increase in the rate of 5-HT synthesis in the rat brain (Johnson *et al.*, 1972). It was also demonstrated that increases in 5-HT synthesis and an increased concentration of 5-HIAA accompanying inhibition of brain dopamine β-hydroxylase in rats also have associated elevation of tryptophan level (Johnson and Kim, 1973). These results may indicate that in some parts of the brain NA plays a regulatory role in the synthesis of 5-HT through a feedback mechanism. Other more direct evidence strongly supports the hypothesis of an interaction between the 5-HT and NA systems. The destruction of catecholaminergic neurons by 6-hydroxydopamine (6-OH-DA) injected intracisternally in rats produces a substantial increase in the rate of 5-HT synthesis as well increasing the concentration of 5-HIAA in the telencephalon (Blondaux *et al.*, 1973). In cats, 5-HT synthesis is markedly increased after treatment with α-methyltyrosine (αMT), an inhibitor of the biosynthesis of catecholamines (Jouvet, 1973). Furthermore, electrolytic lesions of the caudal portion of ascending NA corti-

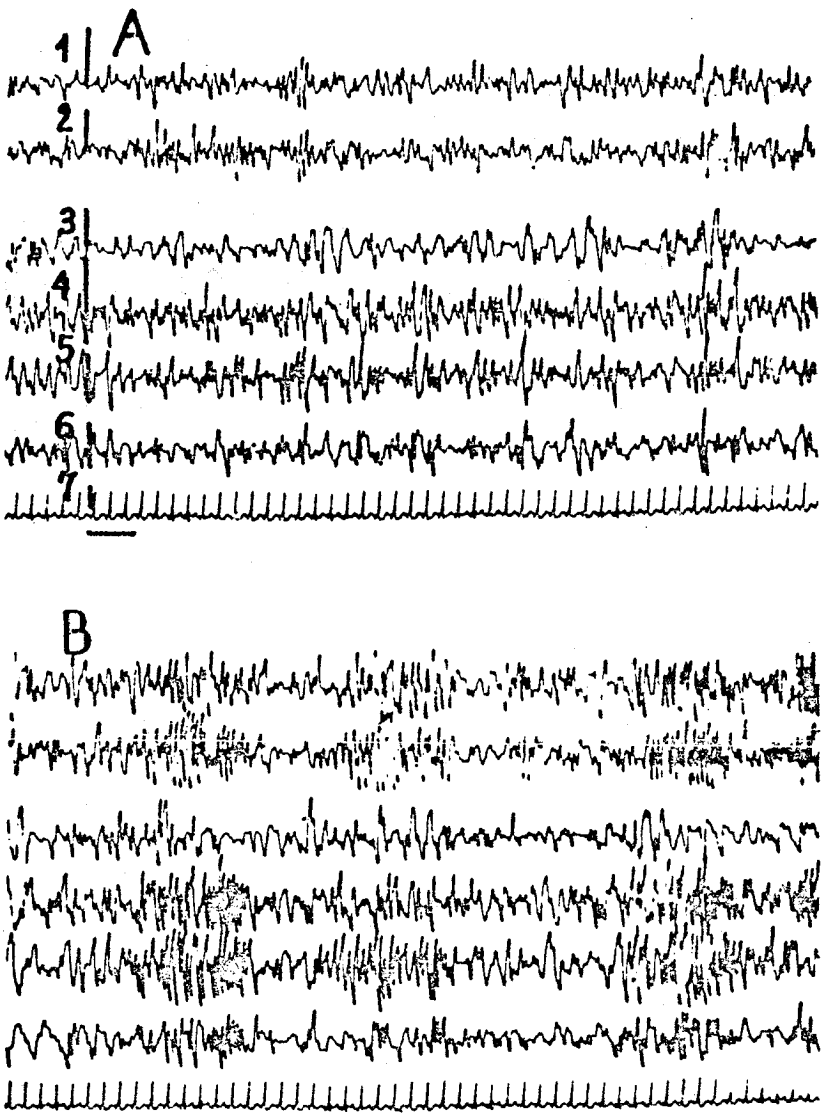
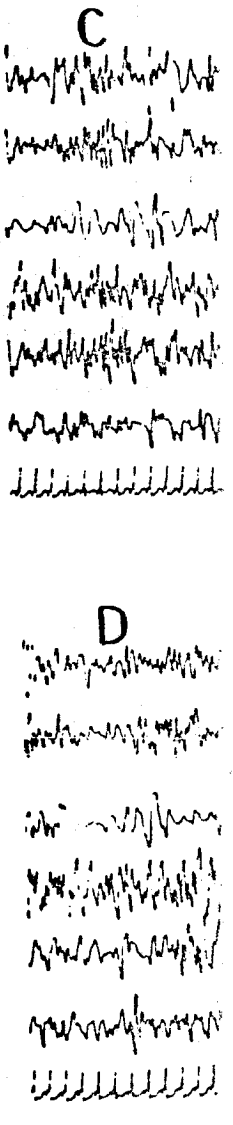


Fig. 1. Effect of dopamine (330 ug) injected into the midline pontine area (corresponding to nucleus raphé magnus). 1, 2, and 3 = frontal, parietal, and occipital leads, respectively, 4 = dorsal hippocampus (right side), 5 = caudate nucleus (left side), 6 = pontine raphé, 7-EKKG. Calibra-



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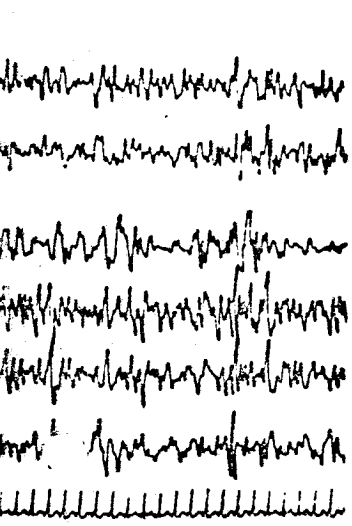

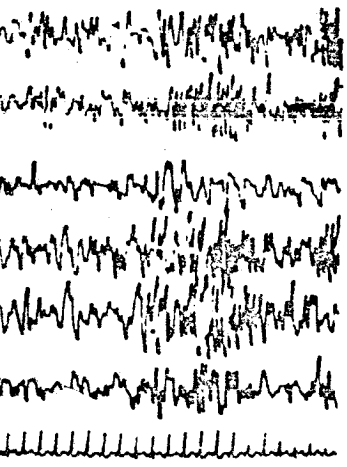

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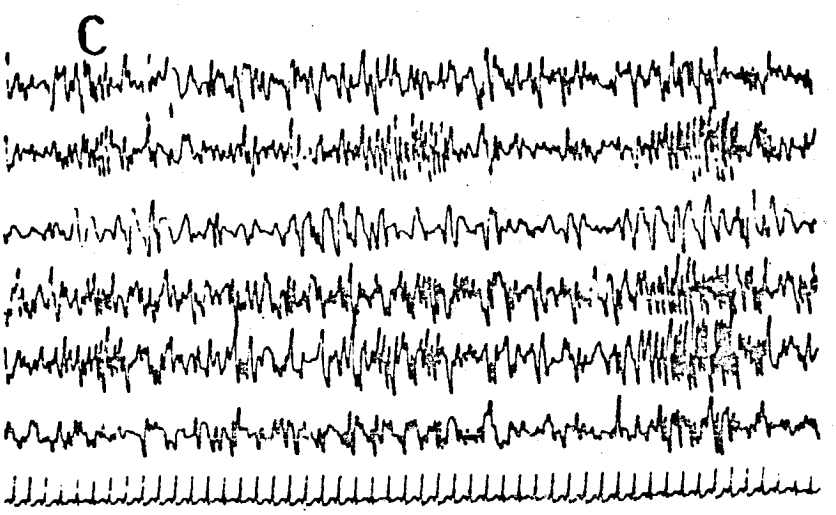

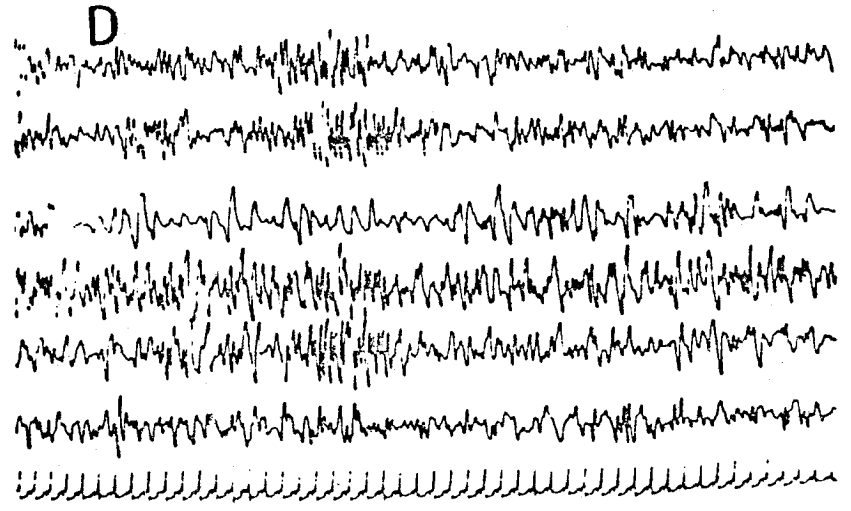

tion 100 uV and 1 second. Note synchronization after administration of DA (For details see Kostowski W. and Gumulka, W. *Pol. J. Pharmacol. Pharm.*, 1974, 26:351-368.)

cal projections of the rostral third of the LC induces a significant increase of both tryptophan and 5-HIAA levels in the telencephalon of the cat. These data suggest that the destruction of the ascending NA system results in an increased turnover of brain 5-HT (Petitjean, 1970; Petitjean and Jouvet, 1970). In rats, bilateral lesions of LC produced a substantial increase in the the forebrain concentration of 5-HIAA 4 days later (Kostowski *et al.*, 1974). However, this effect does not apparently seems to be correlated with a decrease in NA concentration since only a slight decrease of this amine within the cortex and the hippocampus was found at this time. It is also possible that a two-way interaction between the raphé and LC may well exist. Lesions of MR (involving nucleus raphé medianus) induce the significant increase in concentration of 3-methoxy-4-hydroxy-phenylglycol sulfate (MOPEG-SO_4), a metabolite of NA in the cortex and hippocampus (Kostowski et al., 1974; see Table II). This change occurs 4 days following the lesion. Some unknown compensatory mechanisms apparently exist since 10 days after he lesion no changes in MOPEG-SO_4 concentration were observed. The data reported here indicate that interactions between the raphé and LC seems to be reciprocal.

Lesions of raphé produce a well-known insomnia and motor hyperactivity in both cats and rats (Jouvet, 1972; Kostowski *et al.*, 1968). It may be postulated that this phenomenon is at least partially due to the hyperactivity of the NA system since it can be blocked by MT and easily reversed to sedation (Jouvet, 1972; Kostowski *et al.*, 1974a). Lesions of NA pathways and the LC generally cause opposite effects to those resulting from lesions ofthe raphé system. After the destruction of the dorsal NA pathway in cats hypersomnia has been observed (Petitjean and Jouvet, 1970; Petitjean, 1970). As previously mentioned, in these cats an increase in telencephalic 5-HIAA and tryptophan paralleled the decrease of NA. Jones *et al.* (1969) reported that coagulation of the dorsal NA bundle and the A-8 groups of cells resulted in a significant decrease in the cortical low-voltage fast activity but with no changes in behavioral and cortical activation after sensory stimulation. It is postulated that in rats some behavioral changes induced by bilateral lesions of the NLC, such as somnolence and motor hypofunction, may be related to an increased activity of the 5-HT system since they could be blocked to pCPA or by simultaneous lesions of the midbrain raphé (Kostowski, Dománska, and Tarchalska, 1974, unpublished data).

The general conclusion is that serotonergic system of the raphé and noradrenergic systems of the LC may reciprocally inhibit one another. Other evidence concerning the sleep–wakefulness cycle that supports this hypothesis will be reported in the subsequent section of this chapter.

Table II
Biochemical Changes after Lesions of the Locus Coeruleus (NLC) and Ventral Raphé (VR) in Rats

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Table II
Biochemical Changes after Lesions of the Locus Coeruleus (NLC) and Ventral Raphé (VR) in Rats

Experimental groups	Days after surgery	Brain levels ng/g ± S.E.					
		Forebrain			Cortex + Hippocampus		
		5-HT	5-HIAA		NA	MOPEG-SO_4	
(1) Sham lesioned	4	346 ± 10 (12)	236 ± 14 (12)		271 ± 14 (7)	136 ± 8 (7)	
	10	360 ± 19 (9)	286 ± 10 (9)		270 ± 30 (5)	133 ± 5 (9)	
(2) VR lesioned	4	194 ± 14* (6)	187 ± 10 (4)		247 ± 18 (4)	256 ± 15* (7)	
	10	199 ± 12* (5)	156 ± 12* (6)		256 ± 20 (4)	142 ± 5 (5)	
(3) Bilaterally NLC lesioned	4	310 ± 17 (7)	341 ± 22* (10)		205 ± 2* (5)	119 ± 9 (7)	
	10	364 ± 31 (7)	314 ± 14 (7)		127 ± 8* (4)	67 ± 7* (8)	

Numbers of animals for each experiment are reported in brackets.
* = $p < 0.01$ with respect to sham lesioned.
o = $p < 0.05$ with respect to sham lesioned.
p values were calculated by the Student's t test or by the Cochran test for samples with eterogeneous variances.

C. THE SLEEP—WAKING CYCLE AND BRAIN MONOAMINERGIC INTERACTIONS

According to Jouvet (1972, 1973) the ascending NA system is responsible for tonic cortical activation during wakefulness and PS. The 5-HT system of the raphé seems to be responsible for SWS and for "priming" PS while the "executive" mechanisms of the PS appear related to NA neurons. Thus, two antagonistic 5-HT and NA systems are implicated in the mechanisms of cortical desynchronization and synchronization. As mentioned before, insomnia may be induced by lesions of 5-HT neurons or after inhibition of synthesis of 5-HT) as well as by the activation of the NA ascending system (see Jouvet, 1972). PS is accompanied by some phasic electrical phenomena such as pontogeniculo-occipital waves (PGO). Numerous drugs acting upon monoamines may dissociate the appearance of the PGO from the PS stage. Reserpine given in the doses of 0.5–1.0 mg/kg induces a continuous PGO after a latency of about 60 minutes (Delorme *et al.*, 1965; Jouvet, 1972). PGO waves may even be recorded in acute experiments with curarized animals (Jeannerod, 1965). *pCPA* and p-chloromethamphetamine have also been found to "trigger" PGO-like activity similarly to reserpine (Delorme *et al.*, 1965). Furthermore, the effects of pCPA as well as reserpine can be reversed by 5-HTP (Jouvet, 1967a,b; Dement, 1969, Dement *et al.*, 1969 1972; Jacobs *et al.*, 1972). 5-HT appears to inhibit the occurrence of PGO waves since they appear continously after lesions of the raphé system and, as previously mentioned, after inhibition of 5-HT synthesis (Jouvet, 1967, Dement *et al.*, 1969, 1973; Morgane and Stern, 1973). On the other hand, the coagulation of the dorsolateral pontine tegmentum at the level of LC, or injections of 6-OH-DA to this area supress the cortical and geniculate PGO (Buguet, 1969; Buguet *et al.*, 1970; Jouvet, 1972). Intraventricular injections of 6-OH-DA in the cat also reduce the frequency of PGO during the PS stage (see Jouvet, 1972). According to Jouvet (1972) some catecholamine metabolites could be responsible for the triggering of PGO. Catecholamine-containing neurons of the LC are responsible for the release of some deaminated metabolites which trigger postsynaptic responses in the vestibular and oculomotor nuclei, leading to rapid eye movements during PS. Similar events occur in the lateral geniculate and occipital cortex. It is assumed that the serotonergic system of the raphé exerts tonic inhibition upon catecholaminergic mechanisms triggering the phasic phenomena of PS. There, however, are many data which conflict with such model. Morgane and Stern (1973) found that following injection of 75 mg/kg of MT NA level was lowered by 30 to 50% in most regions of the brain but the number of PGO spikes was increased. Henriksen and Dement (c.f. Dement *et al.*, 1973) have reported that MT caused an increase in amount of PS. This

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compound failed to suppress PGO-like waves in animals treated with reserpine (c.f. Jouvet, 1972). According to Haefely *et al.* (1974) and Jalfre *et al.* (1974) the monoamine systems exert a tonic inhibitory influences up on the PGO-triggering mechanisms. Both 5-HT neurons originating in the raphé system and NA neurons of LC inhibit "pacemaker" and/or "generator" cells for PGO waves (see Jalfre *et al.*, 1974). It is also possible that other mechanisms (e.g., cholinergic) also play a role in both triggering and maintenance of PGO waves, however, the 5-HT and NA systems seem to be extensively involved in regulation of these phenomena.

LSD-25 which strongly depresses the firing of raphé cells (Aghajanian *et al.*, 1970) is known to increase the occurrence of PGO in the waking state and during SWS (Morgane and Stern, 1972). It has been also reported that minute doses of this compound applied directly to the nucleus raphé dorsalis increase PGO spikes outside of the PS. Recently we have found (Kostowski *et al.*, 1974a) that 5-HT and quipazine, a compound with 5-HT like activity, injected bilaterally to the LC supressed PGO waves induced by reserpine in cats (Fig. 2). According to Brooks *et al.* (1972). Dement (1969), and Delorme *et al.* (1966) depletion of 5-HT is of significance in the genesis of PGO waves induced by reserpine. If it is accepted that the LC system is involved in the regulation of geniculate discharges our finding may indicate that 5-HT inhibits the activity of those catecholamine-containing cells of the LC involved with the neuronal mechanism underlying the generation of PGO waves. In fact, it was observed that the bioelectrical activity of some cells in this area is decreased during SWS, the phase strongly related to the 5-HT system of the raphé (Lidbrink *et al.*, 1973). It was also observed that electrical stimulation of the raphé dorsalis caused a complete suppression of geniculate PGO waves. This

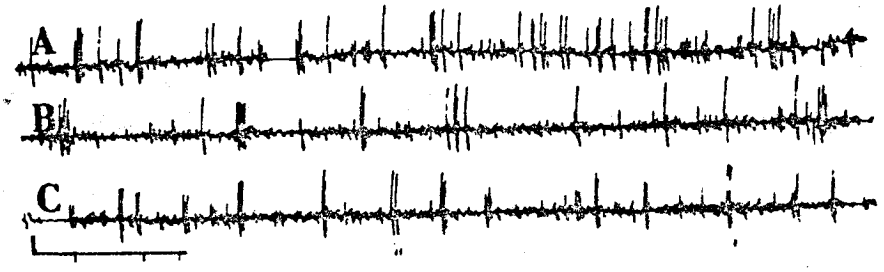

Fig.2. Effect of serotonin (10 ug) injected bilateraly into the nucleus locus coerleus on reserpine-induced PGO-like activty in the lateral geniculate nucs of the cat. A = control pattern, B = 5 minutes after serotonin, C = 15 minutes after serotonin. Calibration 100 uV and 20 second (For details see Kostowski, W., Gumulka, W., and Domańska, M., 1974, Communications of Symposium—Serotonin, brain, drugs, Kazimierz, 15–16 October, 1974.)

stimulation was ineffective in suppressing PGO waves when delivered to other nuclei of the raphé (nucl. raphé pontis and magnus; see Dement *et al.*, 1973). On the other hand some raphé units are inhibited during PS. McGinty and Harper (1973) studied the activity of cells in the dorsal raphé and clearly observed an inhibition of the regular firing of these units during PS and in SWS preceding waves in the lateral geniculate nucleus.

Interactions between 5-HT and NA systems seem to be one of the most important mechanism regulating the sleep–wakefulness cycle. When SWS is initiated the mechanisms involved in PS are inhibited and vice versa. Such a model is generally accepted by majority of investigators although many discrepancies exist concerning the details of this phenomenon. A feedback mechanism between MA systems as the basis of sleep–waking regulation has been recently postulated (Jouvet, 1972, 1973; Dement *et al.*, 1973; Routtenberg, 1973). Special attention is paid to the negative feedback from the LC to the raphé and from the raphé to the LC. According to a model proposed by Routtenberg (1973) the raphé controls and is controlled by the LC. On the other hand the neocortex is controlled by the raphé system (and controls the raphé). Such a model is generally in agreement with the well-known theory of Jouvet and is compatible with the original theories of Hernandez-Peon (1964,1965a,b), Clemente *et al.* (1963), and Nauta *et al.* (1966) of forebrain–brainstem circuits regulating sleep and wakefulness states. Routtenberg (1973) postulates that oscillations in the levels of 5-HT and the catecholamines lead to oscillations in the stages of sleep. According to this model wakefulness—resulting from inhibition of the SWS system—leads to a "buildup" of 5-HT within the raphé perikarya and terminals. Then 5-HT, after reaching a "critical" level, suppresses the activity of the LC, noradrenergic system. This negative feedback from the raphé to the LC, because of inhibition of neuronal activity, causes a "buildup" of catecholamines to some "critical" level. Then, the LC would begin to exert an inhibitory influence upon the raphé. Since the activity of 5-HT cells would be decreased a "buildup" of 5-HT in the raphé begins. This neurohormone then reaches a critical level for the release of SWS and the sleep cycle would begin over again (see Fig. 3). Thus, there should be a reduced turnover of 5-HT in the raphé preceding SWS and a reduced turnover of NA in the LC preceding PS (Routtenberg, 1973). This interesting model required further investigation, although it should be mentioned, however, that Pujol *et al.* (1968) have demonstrated an increased NA turnover in rats during PS.

The model described above does not explain the role of the DA system in the sleep–wakefulness cycle. This system as well as the NA system is extensively involved in the regulation of waking mechanisms. Jouvet (1972) and other

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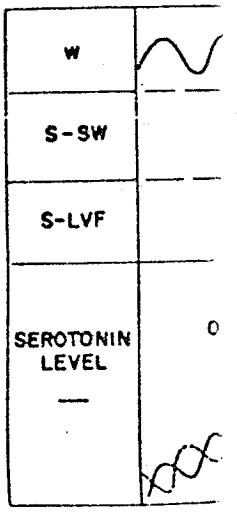

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authors (Jones *et al.*, 1973) postulate that the DA nigrostriatal system may be involved in behavioral arousal and responsiveness, while the ascending NA system is involved in tonic electrocortical activation. We believe that possible inhibitory influences from the LC on the raphé and inhibition of nigrostriatal DA system by the raphé (Kostowski *et al.*, 1972; Gumulka *et al.*, 1973) offer some partial explanations for the complexity of the PS stage. The inhibition of the 5-HT system of the raphé by the LC reduces the signs of SWS and, consequently releases the nigrostriatal DA system from the inhibitory influencies of the raphé. Thus, both the waking system and the PS system might be active during PS however, well-organized motor behavior characteristic of the waking stage is inhibited by muscle relaxation probably mediated by caudal portions of the LC (Jouver, 1972; Dement *et al.*, 1973). The model I wish to propose is schematically summarized in Fig. 4. These speculations will obviously require further studies; particularly, interactions between the 5-HT system of the raphé and the DA nigrostriatal system should be extensively analyzed using biochemical, behavioral, and bioelectrical methods.

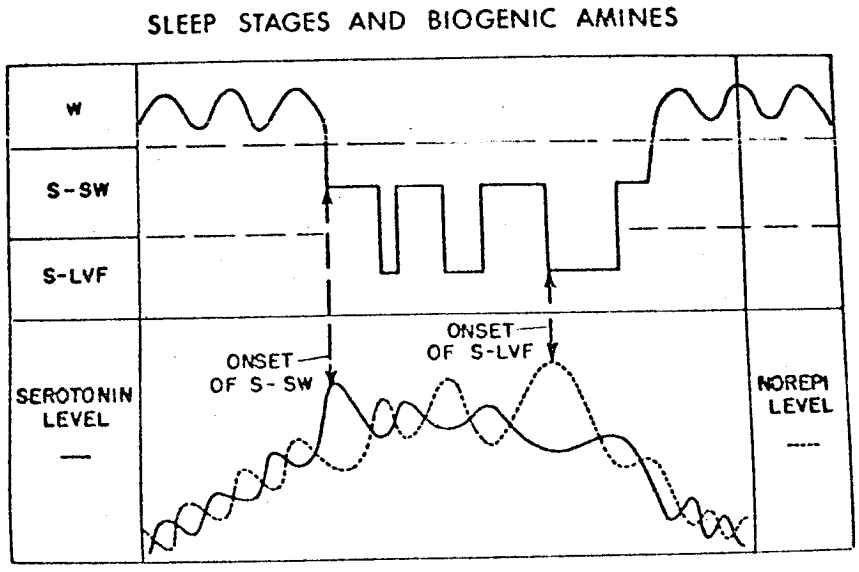

Fig. 3. Hypothetical changes in 5-HT and NA levels and variations within each level as rellatded to stages of wakefulness (W), sleep with slow waves (S-SW) and paradoxical sleep (low voltage fast activity S-LFV). (Routtenberg, A. In: *Neural Systems and Circuitry Concerned with Sleep-Waking Behaviour*, edited by P.J. Morgane and W.C. Stern, Brain Information Service, Res. Report Nr 2, Univ. Calif., Los Angeles, pp. 33–38.)

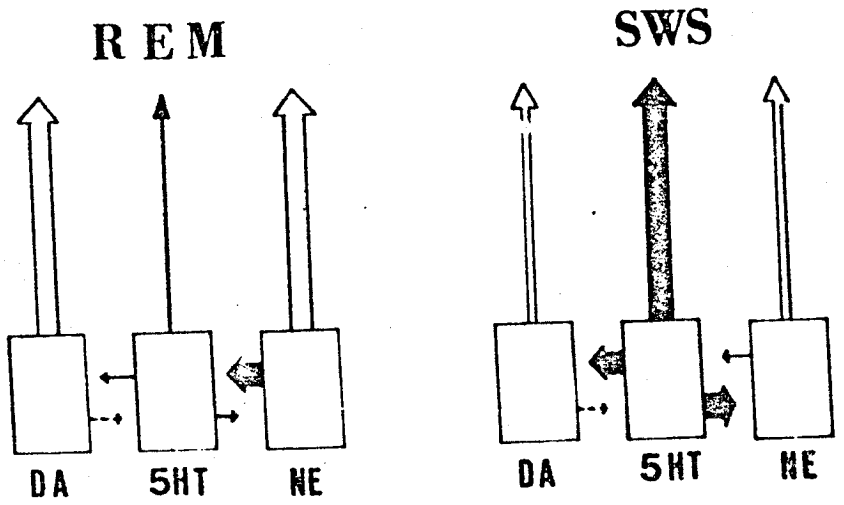

Fig. 4. Schema of brain mechanisms of sleep showing a feedback relationship between serotonergic system of the raphé (5-HT), the noradrenergic system of the locus coeruleus (NE) and the dopaminergic nigrostriatal system (DA). White arrows–"activation", black–"inhibition", dashed–unknown influences. The DA system is supposed to be involved in behavioral arousal during waking state, the NE system controls EEG arousal mechanisms in both waking and rapid eye movent sleep (paradoxical sleep, REM). The 5-HT system of raphé is involvedd in behavioral inhibition and cortical synchronization and controls slow wave sleep (SWS). During SWS the 5-HT system inhibits both the DA and NA systems. During REM negative feedback from NA system causes suppression of 5-HT-system activity and consequently releases DA system from inhibitory control of raphé. Thus both the NA and the DA system might be active during REM; however, well-organized motor behavior characteristic of the waking stage is probably inhibited due to muscular relaxation mediated by caudal portions of the locus coeruleus (see text).

D. OPERANT BEHAVIOR, AGGRESSIVE, AND BRAIN MA INTERACTIONS

The antagonistic effects of the 5-HT and NA systems are also well known in studies utilizing operant conditioning methodologies. The findings of Stein (1968), Wise and Stein (1969), and Wise *et al.* (1973) support the idea that behavior may be facilitated by an α-noradrenergic reward system and suppressed by a serotonergic punishment system. These systems appear to function reciprocally in the control of goal-directed behavior (Fig. 5). Evidence that the NA system is involved in reward mechanisms has been extensively summarized by Stein (1968), Arbuthnott *et al.* (1970), Berger *et al.* (1971), Wise and Stein (1969). According to Wise *et al.* (1973), the 5-HT system could appose the NA reward system and thereby inhibit goal-directed behavior.

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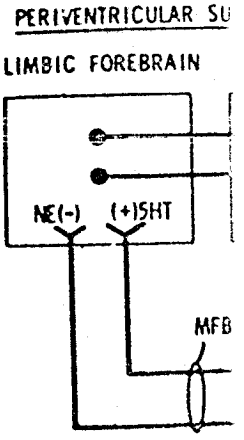

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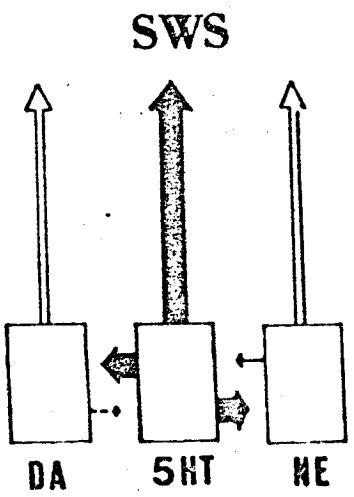

f sleep showing a feedback relationship between noradrenergic system of the locus coeruleus (NE) and . White arrows–"activation", black–"inhibition", m is supposed to be involved in behavioral arousal EEG arousal mechanisms in both waking and rapid The 5-HT system of raphé is involvedd in behavioral controls slow wave sleep (SWS). During SWS the systems. During REM negative feedback from NA activity and consequently releases DA system from A and the DA system might be active during REM; aracteristic of the waking stage is probably inhibited udal portions of the locus coeruleus (see text).

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Intraventricular administration of 1-NA facilitated bar-pressing for hypothalamic self-stimulation. The role of the LC in the mechanism of positive reinforcement has been recently established by Arbuthnott *et al.* (1970, 1971). Depletion of brain 5-HT by treatment with pCPA has been reported to facilitate self-stimulation (Poschel and Niteman, 1971). Intraventricular injections of 5-HT as well as an α-blocking drug, phentolamine cause suppression of self-stimulation and increased the suppression of punished behavior (Wise *et al.*, 1973). It should also be pointed out that dopaminergic receptors have been recently reported to play a role in reward mechanisms (Clavier and Routtenberg, 1974; Kadzielawa, 1974). L-Dopa and apomorphine increased the rate of self-stimulation, and these effects were antagonized by haloperidol (Kadzielawa, 1974). These findings support the concept that the catecholaminergic systems in the brain may facilitate behavior and the 5-HT system can suppress it (Wise *et al.*, 1973).

Finally, the antagonistic role of 5-HT and catecholamines may be mentioned with respect to aggressive behavior. The discussion of this problem exceeds the limits of the present discussion however, some findings, should be mentioned. After administration of pCPA increased aggressive behavior as well as inten-

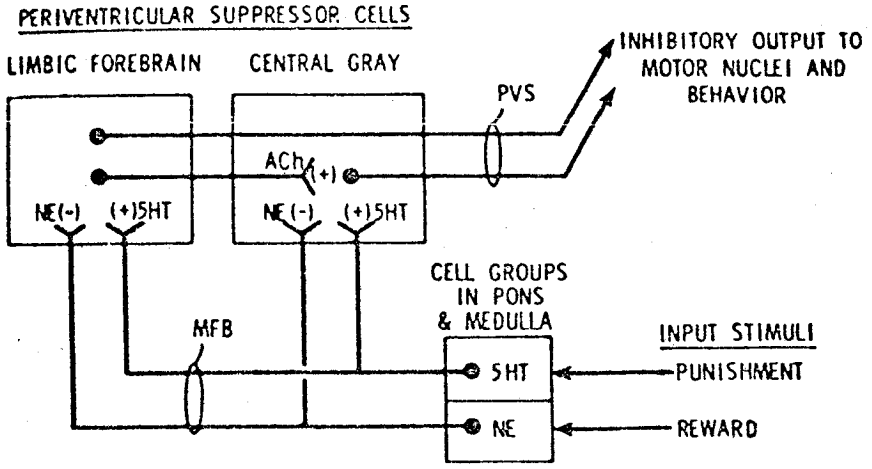

Fig. 5. Diagram showing the hypothetical relationship between reward and punishment mechanisms and behavior. Signals of positive reinforcement release behavior from periventricular cholinergic system suppression due to an inhibition mediated by noradrenaline (NA). Signals of punishment og failure to increase behavioral suppression by activation 5-HT-cells of raphé (and probably other 5-HT cell groups). Thus, NE inhibits and 5-HT excited the periventricular system suppressor cells (PVS). MFB medial forebrain bundle. (Wise, C.D. Berger, B.D., and Stein, L., *Biol. Psychiat.* 1973, 6:3-21.)

sified sexual behavior was observed in rats (Karli *et al.*, 1969; Sheard, 1969; Shillito, 1969; Tagliamonte *et al.*, 1969) and in cats (Ferguson *et al.*, 1970). pCPA not only increases mouse-killing behavior in rats (Sheard, 1969, 1973), but also potentiates the muricidal effects produced by removal of the olfactory bulbs (DiChiara *et al.*, 1971). Lesions of the dorsal and medial raphé nuclei have been reported to induce mouse-killing behavior in naturally nonkilling rats (Vergnes *et al.*, 1973; Grant *et al.*, 1973). Since the time-course of this mouse-killing behavior was paralleled by a progressive reduction in brain 5-HT one may assume that this neurohormone contributes to an inhibitory effect upon aggressive behavior (Grant *et al.*, 1963). On the other hand, other investigators did not observe mouse-killing behavior in rats induced following lesions of the raphé system (Sheard, 1973; Kostowski *et al.*, 1974b). It was observed by Benkert *et al.* (1973) that fighting and mounting behavior occurred when the catecholamine level of the brain was high and 5-HT content was markedly reduced. These results were based upon experiments in which MA levels were altered in animals treated with pCPA, L-dopa, reserpine, and RO-4-4602 (an inhibitor of dopa decarboxylase) in various combinations. Thus, catecholamines (particularly DA) and 5-HT seem to play antagonistic roles in the regulation of aggressive and sexual behavior.

E. SUMMARY

Interactions between brain monoaminergic systems have been recently investigated by several authors. The data concerning such interactions offer new hypotheses for the clarification of sleep–waking cycle mechanisms, reward and punishment mechanisms, emotional behavior, and the regulation of motor activity.

With histofluorescence methods numerous anatomical connections between serotonergic systems of the raphé, noradrenergic systems of the locus coeruleus and the dopaminergic nigrostriatal pathways have been detailed. The medial and ventral portions of the locus coeruleus provide projections to the raphé; projections from the raphé to the locus coeruleus, however, have not been definitively established. It is also known that some dopaminergic cell bodies, probably grouped within the substantia nigra, send their axons toward the raphé. On the other hand, numerous serotonergic terminals were localized in the substantia nigra.

Lesions of the raphé system increase the effects of amphetamine but decrease or block the cataleptogenic effects of neuroleptics. These and other data indicate that lesions of the serotonergoc system of the raphé lead to an increased reactivity of the dopaminergic nigrostriatal pathway. Thus, it may be hypothesized that the raphé exerts excitatory influences upon the dopaminergic

system. It is also known that lesions of the locus coeruleus lead to a increased turnover of brain serotonin and lesions of the raphé probably increase brain NA turnover.

Injections of serotonin into the locus coeruleus inhibit PGO-like activity evoked by reserpine in cats. In summary, these and other experimental data suggest that the locus coeruleus and raphé reciprocally inhibit one another.

Interactions between the serotonergic and noradrenergic systems seem to be one of the most important mechanism regulating the sleep–wakefulness cycle. A model of a sleep–waking regulatory mechanism, based upon interactions among the raphé, locus coeruleus, and the dopaminergic nigrostriatal systexshas been described.

The antagonistic effects of the serotonergic and noradrenergic systems as a potential basis for reward and punishment mechanisms have been briefly considered. Some attention has also been given to an opposing role for serotonin and catecholamines in the mechanisms concerned with aggressive behavior.

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