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TOPIC ACTION OF PSYCHOTROPIC DRUGS ON THE ELECTRICAL ACTIVITY OF CORTEX, RHINENCEPHALON AND MESODIENCEPHALON

(EXCITEMENT, TRANQUILLIZATION, SEDATION AND SLEEP)

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The purpose of our investigations, carried out with Dr. H. GANGLOFF AND R. TISSOT, was to correlate *functional states* induced by drugs—excitement, tranquillization or sleep—with definite *electrographic patterns* and brain structures.

The drugs were grouped according to their somatic and visceral symptoms in the following categories: (1) Specific ergotropic drugs with sympathetic symptoms; (2) Specific trophotropic drugs with parasympathetic symptoms; (3) Trophotropic tranquillizers with hypnotic action; (4) Real tranquillizers without important hypnotic action; (5) Sedatives and hypnotics.

METHODS

Our stereotaxic technique for derivation and stimulation of cortical or subcortical brain structures in the unanesthetized rabbit has already been described (GANGLOFF AND MONNIER[6,9–12]).

A stereotaxic socklet screwed on the skull under local anesthesia is used. The electrical brain activity is lead simultaneously from the motor, sensory and visual cortex of both hemispheres with epidural silver electrodes, and from the rhinencephalon (hippocampus), caudate nucleus, medial and lateral thalamus, and midbrain reticular formation, with deeply implanted silver needle electrodes. At the same time the cardiac and respiratory rates are recorded. Bipolar electrical stimulation is performed with the stimulator of O. A. M. Wyss in the medial thalamus (intralaminary system), lateral thalamus (dorsally and ventrally), rhinencephalon (dorsal hippocampus), and midbrain reticular formation, with steel needle electrodes. Stimuli of various frequencies, duration, and voltage, are applied according to the structure.

The following *parameters* were used for analyzing the pharmacological action:

(1) Somatic and visceral behaviour, including heart activity and respiration.

(2) Spontaneous electrical brain activity of the cortex and subcortex, showing alternating episodes of relaxation and arousal (Fig. 1).

(3) Electrographic "attention" reaction evoked by external stimuli, especially by noise and human presence (Fig. 2a).

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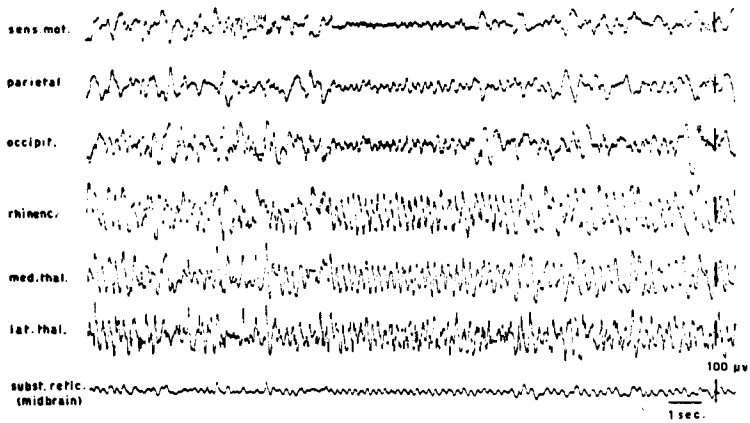

Fig. 1. Spontaneous electrical brain activity of the unanesthetized rabbit. Alternating sleep-like pattern and arousal pattern.

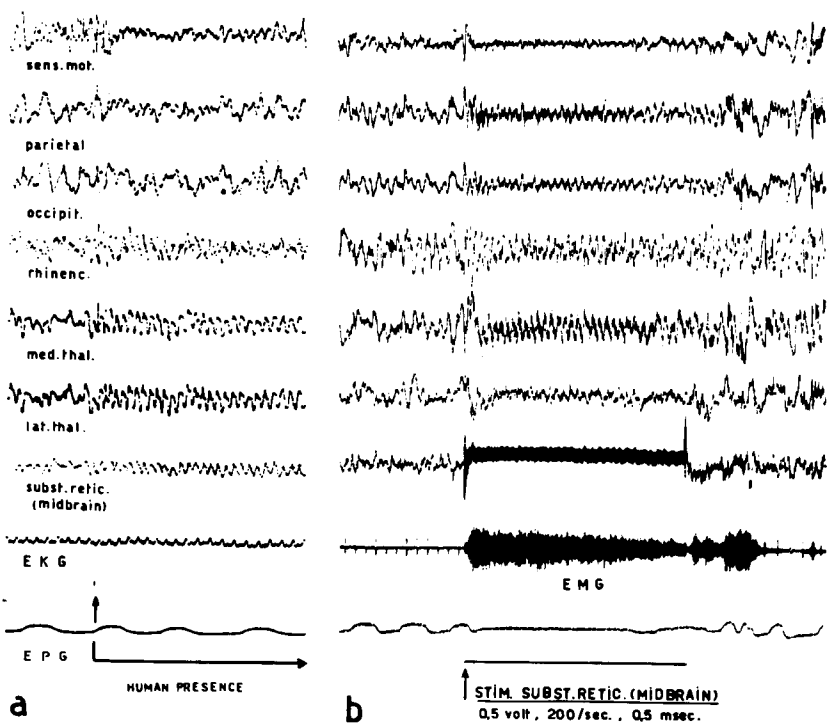

Fig. 2. (a) "Attention reaction" to human presence. (b) "Arousal reaction" to electrical stimulation of the midbrain reticular formation at 200/sec. Muscle activity with apnea.

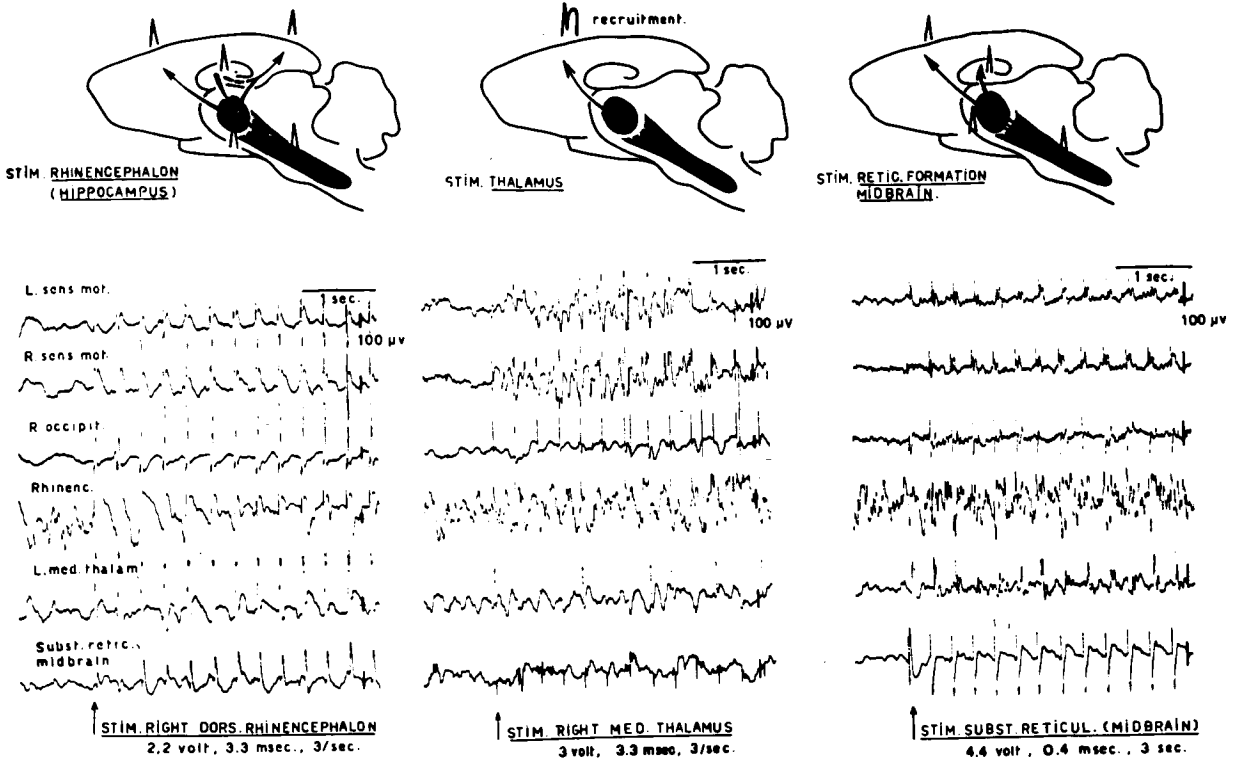

Fig. 3. Electrographic discharge pattern in cortex, rhinencephalon, thalamus and midbrain reticular formation during stimulation of rhinencephalon (medial thalamus and midbrain reticular formation).

(4) Electrographic "arousal" reaction evoked by electrical stimulation (200 sec) of the midbrain reticular formation (Fig. 2b).

(5) Electrographic discharge pattern evoked in the cortex and subcortex by electrical stimulation of the midbrain reticular formation, thalamic intralaminary system, and rhinencephalon at low frequency (3 sec) (Fig. 3).

(6) Electrographic after-discharge induced by electrical stimulation of the motor-sensory cortex, lateral thalamus and rhinencephalon, at middle frequency (40 sec) (Fig. 4).

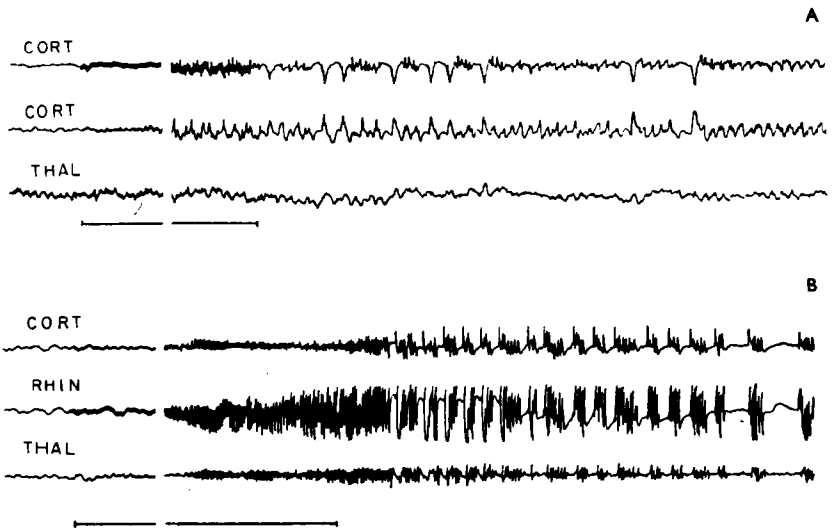

Fig. 4. Electrographic after-discharge pattern induced by stimulation of thalamus (A) and rhinencephalon (B) at 1 volt, 40 impulses/sec.

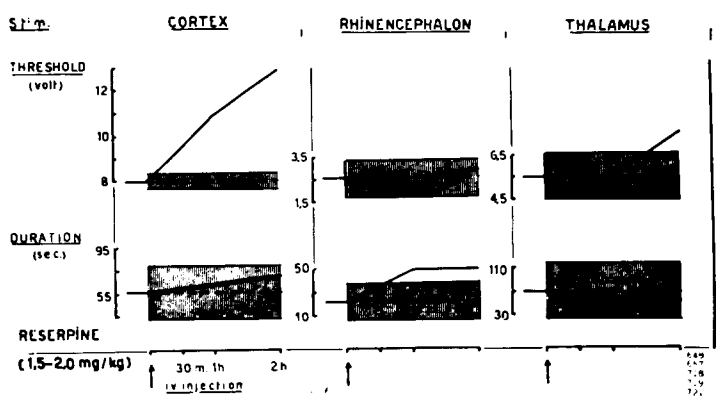

Fig. 5. Threshold in volts and duration in seconds of the after-discharge evoked by stimulation of cortex, rhinencephalon and thalamus 30 min, 1 and 2 hours after injection of reserpine.

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The threshold of the discharges and after-discharges is measured in volts and their duration in seconds. The values are compared with average values determined statistically in normal animals (Fig. 5).

In all experiments unanesthetized rabbits with an average weight of 2.5 to 3.0 kg were used, and the drugs were injected intravenously (2–5 ml per injection within 60 sec). The electrical brain activity as well as the cardiac and respiratory rates were recorded on a Schwarzer 16-channels electroencephalograph.

RESULTS

1. *Specific ergotropic drugs with sympathetic symptoms*

Drugs inducing ergotropic states, activate simultaneously the sympathetic-adrenergic system, and the reactivity of the whole somatic system including the emotional and psychic behaviour. This is the case of *cocaine hydrochloricum* (25 mg/kg), *d-amphetamine* (1 mg/kg), *d-lysergic acid diethylamide* (25, 35, 50 gamma/kg) and *levallorphan*, an antagonist of morphine (0.2–0.8 mg/kg; 6–15 mg/kg). The changes in behaviour consist of somatic symptoms such as arousal, wakefulness, increased reactivity to

TABLE I

Parameters			*Ergotropic drugs*		
			Cocaine Amphetamine	*LSD*	*Levallorphan*
Behaviour	somatic		Alertness	Excitement	Alertness
	visceral		Mydriasis Tachycardia	Mydriasis, Tachypnea Salivation, Chewing	Restlessness
Spontaneous EEG			Arousal	Arousal Subcort. desynchr.	Arousal
"Attention" reaction			—	↑	↑
"Arousal" reaction (Stim. S. reticul)			↑	↑	↑
			Stimulation Rh Th Re	*Stimulation* Rh Th Re	*Stimulation* Rh Th Re
Discharge	*Derivation*	Co	↑ ↓ —	↑ ↓ ↑	↓ ↑
		Cau	↓ ↓ —	↓ ↓ ↓	
		Rh	—		
		Th	↓ ↓ —	↓ ↓	
		Re	↓ —	↓ ○	↓
			Stimulation Co Rh Th	*Stimulation* Co Rh Th	*Stimulation* Co Rh Th
After-discharge	*Derivation*	Thresh. (V)	↑ — —	↑ ↑ ↑	↑ ○ ↑
		Durat. (S)	↓ ↑ —	↑ ○ ↑	↓ ○ ↓

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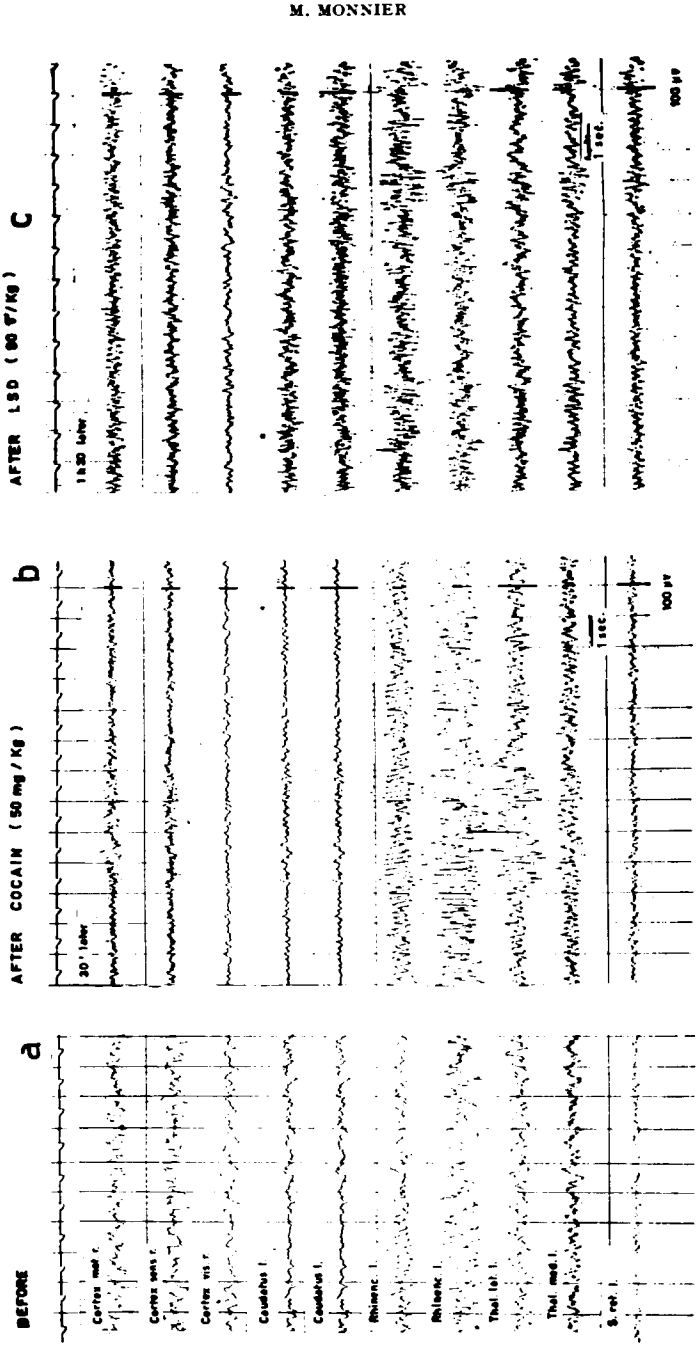

Fig. 6. Alteration of the spontaneous electrical brain activity after injection of cocaine (b) and LSD (c).

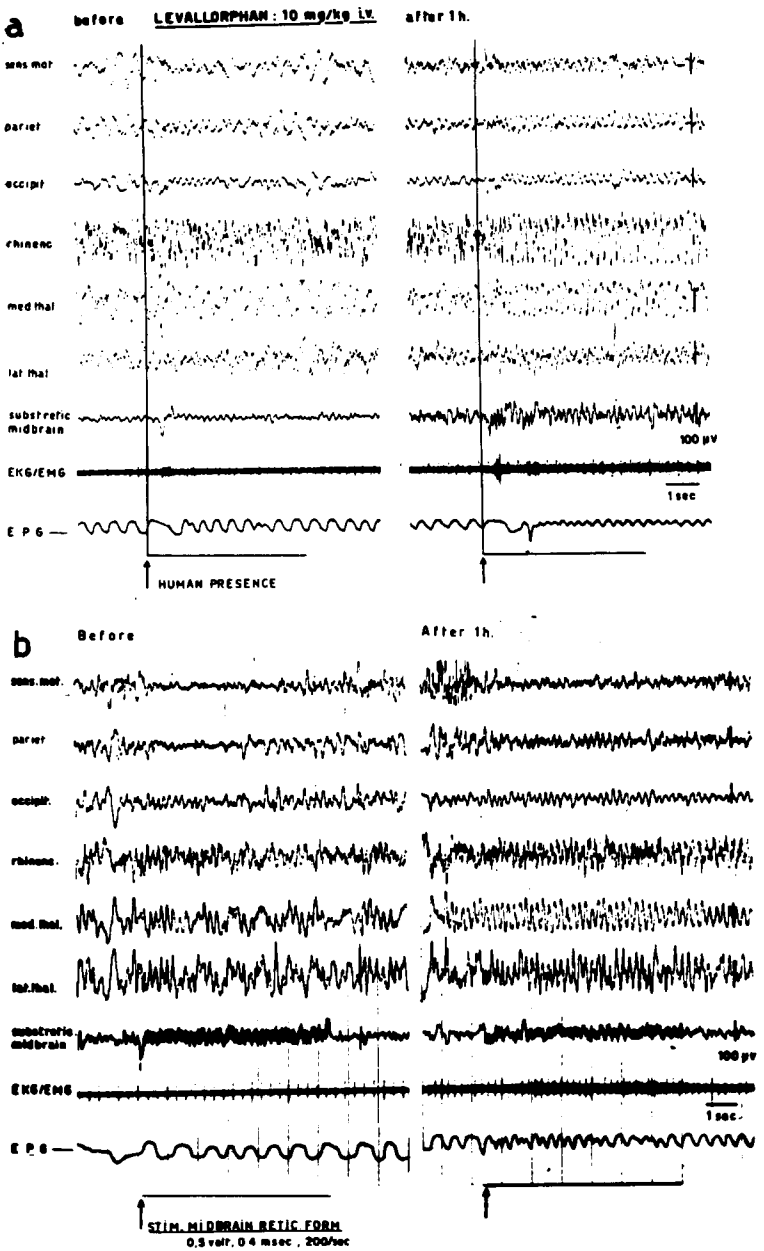

Fig. 7. (a) Increased electrographic attention reaction to human presence and (b) arousal reaction to stimulation of midbrain reticular formation, 1 hour after injection of levallorphan (10 mg/kg).

sensory stimuli, righting of head and ears, movements of nose and mouth (chewing), restlessness, escape reactions. The animal shows on the other hand visceral symptoms such as wide opening of the lids, dilatation of the pupils, blood pressure rise and tachypnea suggesting an increased sympathetic innervation.

Electrographically a typical arousal pattern is observed, with desynchronization of the electrical activity (low voltage fast waves), suppression of the bursts in the motor sensory cortex, and synchronization of the subcortical activities, namely in the thalamus, rhinencephalon and midbrain reticular formation. This synchronization, characterized by a regular rhythm at the frequency 5–7 c/sec, sometimes appears in the parieto-occipital cortex also (Fig. 6b).

The electrographic "attention reaction" to external stimuli (noise) or human presence (Fig. 7a) and the "arousal reaction" induced by stimulation of the midbrain reticular formation are increased (Fig. 7b).

The recruited action of the thalamic intralaminary system on the thalamus and cortex is generally depressed, whereas the ascending impulses (spikes), generated by stimulation of midbrain reticular formation are seldom depressed, and sometimes even enhanced (Fig. 8). The spikes generated by stimulation of the rhinencephalon (Ammon's horn) and propagated to the thalamus and cortex are sometimes depressed after initial facilitation. This depressive action is perhaps responsible for the anti-convulsant properties of the ergotropic psychamines. The thresholds of the after-

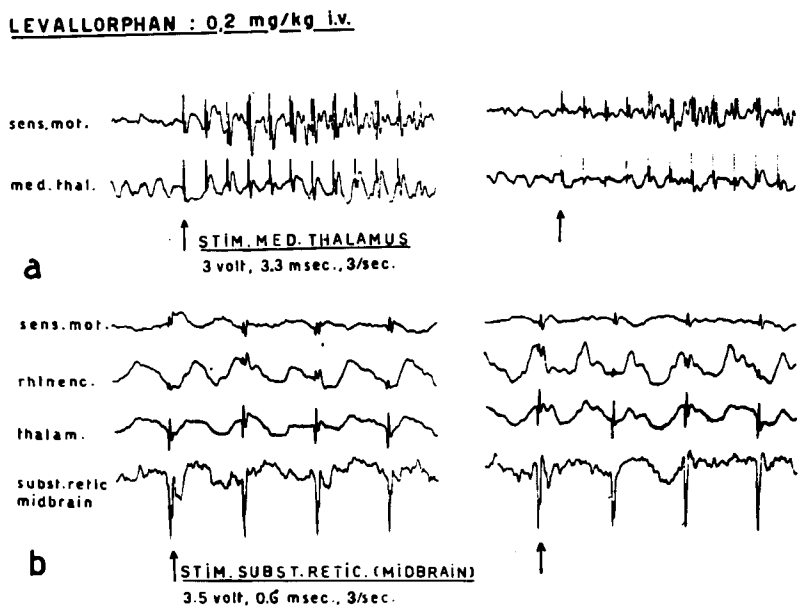

Fig. 8. Depression of the response recruited in cortex and thalamus by stimulation of the media thalamus (a). No depression of the spikes evoked by stimulation of the midbrain reticular formation after injection of levallorphan (0.2 mg/kg) (b).

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discharges induced by stimulation of the cortex, thalamus or rhinencephalon are not significantly altered.

Whereas cocaine and amphetamine elicited a very similar ergotropic behaviour and typical electrographic "arousal pattern", the *d*-lysergic acid derivative produced in the later period a desynchronization of the electrical activity not only in the cortex but also in the subcortex, alternating with spindle-like synchronization episodes. Salivation, chewing, and licking, were often observed (Fig. 6c).

From these various data, we may conclude that *ergotropic drugs* inducing arousal, alertness, excitement, and restlessness with sympathetic visceral symptoms act in the following way: (1) The excitability of the midbrain reticular system is unchanged or increased; (2) The activity of the medial intralaminary thalamic system is depressed: its recruiting action on the cortex decreases; (3) The excitability of the rhinencephalon (Ammon's horn) is depressed, sometimes after an initial increase.

2. Specific trophotropic drugs with parasympathetic symptoms

Drugs inducing trophotropic states activate mainly the parasympathetic system and the mechanisms providing relaxation, protection and nutrition of the "milieu intérieur". *Morphine* (20, 25, 40 mg/kg i.v.) and *levorphan* (10 mg/kg i.v.) may be

TABLE II

Parameters	*Specific trophotropic*	*Trophotropic tranquillizers*		*Sedatives*	*Hypnotics*
	Morphine 20, 25, 40 mg/kg	*Chlorpromazine* 5–10 mg kg	*Reserpine* 0.5–2.0 mg/kg	*Phenobarbital* 20–25 mg/kg	30, 50, 100 mg kg
Behaviour somatic	Drowsiness	Drowsiness Indifference	Indifference	—	Drowsiness Sleep
Behaviour visceral	Myosis Bradycardia				Tachycardia
Spontaneous EEG	Sleep-like	Sleep	Mixed arousal + relaxation		Sleep
"Attention" reaction	↓	↓	↓	—	↓
"Arousal" reaction	↓	↓	(↓)	↑	↓

Discharge	Rh	Th	Re	Rh	Th	Re	Rh	Th	Re	Rh	Th	Re	Rh	Th	Re
Co	·	↑		(↓)	↑	↓	↓	(↑)↓	↓		↓	↓	↑	(↑)↓	
Rh				↑		(↓)	C ↓		—			—	↑		
Th				·		(↑)	·		(↓)		↓	·		(↑)↓	
Re			↓	—		(·)	·		↑			(↑)			

After-discharge	Co	Rh	Th	Co	Rh	Th	Co	Rh	Th	Co	Rh	Th	Co	Rh	Th
Thresh. (Volt)	·	—	—	·	·	·	·	—	·	·	↑	↑	↑	—	↑
Durat. (Sec.)	·	—	↑	·	·	·	—	↑	—						

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regarded as drugs having a specific action on the autonomic system, since they produce (besides analgesia) not only drowsiness or sleep, but also parasympathetic symptoms such as myosis, blood pressure fall, bradycardia and bradypnea.

The electrographic picture consists of a sleep-like generalized slow wave activity, chiefly at higher doses (Fig. 9). The attention reaction and the arousal reaction to stimulation of the reticular formation are depressed or abolished (Fig. 10). The excitability of the rhinencephalon is increased. The spikes induced by stimulation of the rhinencephalon (hippocampus), and their propagation to other structures such as reticular formation, thalamus, and cortex, are enhanced (Fig. 11a). This explains the convulsant action of morphine. The excitability of the thalamic intralaminary system is generally increased, as shown by the enhanced spike and wave complexes recruited bilaterally in the thalamus and cortex by stimulation of the thalamic intralaminary system (Fig. 11b). On the contrary, the spikes evoked by stimulation of the midbrain reticular formation are depressed or suppressed in the reticular formation itself, thalamus, rhinencephalon and cortex (Fig. 11c). Finally, the cortical excitability is decreased (raised threshold of the after-discharge).

The comparison of the electrographic patterns induced by morphine as a trophotropic centrally acting drug inducing drowsiness, sleep, indifference to external stimuli, analgesia and parasympathetic symptoms shows an electrographic picture exactly opposite to that of ergotropic drugs, namely depression of the (midbrain) reticular system, enhancement of the recruiting activity of the medial thalamic intralaminary system, and activation of the rhinencephalon (Table II).

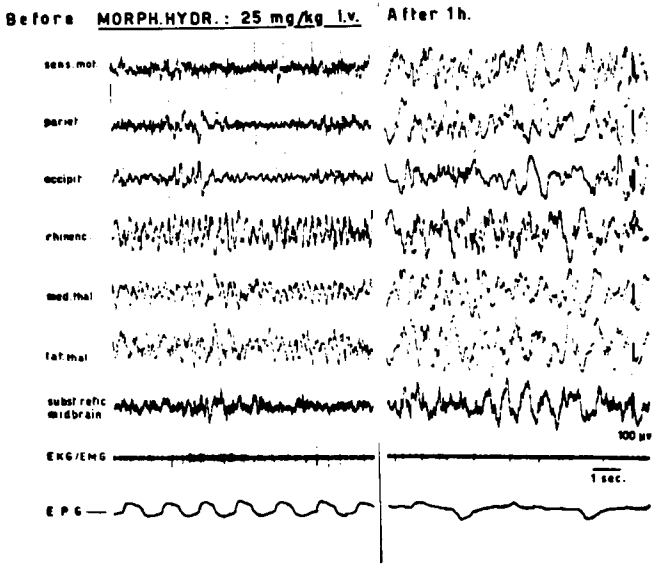

Fig. 9. Sleep-like high voltage slow wave activity, 1 hour after injection of morphine (25 mg/kg).

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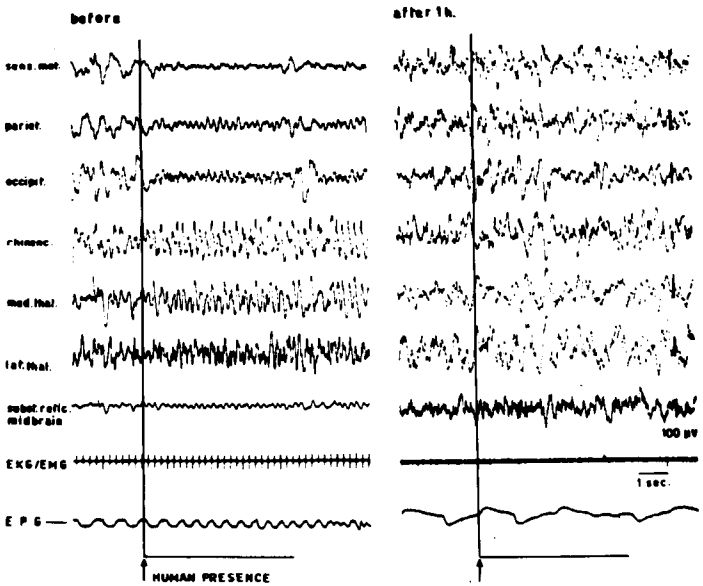

Fig. 10. Suppression of the attention reaction to human presence, 1 hour after injection of morphine (25 mg/kg).

3. *Trophotropic tranquillizers with slight hypnotic action*

Chlorpromazine (5–10 mg/kg) differs from the tranquillizers of the reserpine type by a more pronounced (transitory) sleep-like action, detectable both in the behaviour and on the electrogram (Fig. 12a). Besides its hypnotic tranquillizing action it evokes marked parasympathetic symptoms. The sleep-like effect seems to be associated with an increased recruiting activity of the thalamic intralaminary system on the cortex (Fig. 12b). The increased excitability of the medial thalamus is confirmed furthermore by the decreased threshold of the thalamic after-discharge. A transitory initial depression of the midbrain reticular system (not observed after reserpine) may contribute to the sleep effects as after morphine, with which the drug has common features (Fig. 12c). (It is well known, furthermore, that chlorpromazine potentializes the action of analgesics.) The electrographic attention and arousal reactions are depressed (Fig. 13).

4. *Real tranquillizers without important hypnotic action*

Reserpine (0.5–2 mg kg) and *Serotonin* (0.1–1 mg/kg) may be considered as trophotropic tranquillizers since they produce relaxation, indifference to external stimuli with slight transitory drowsiness, and parasympathetic vegetative symptoms.

Electrographically these drugs do not evoke a "sleep pattern, but the "mixed arousal and relaxation pattern", described by MONNIER AND GANGLOFF[8,11]. They suppress the "attention" reaction to external stimuli and the "arousal reaction" to stimulation of the midbrain reticular formation (Fig. 14). The excitability of the medial

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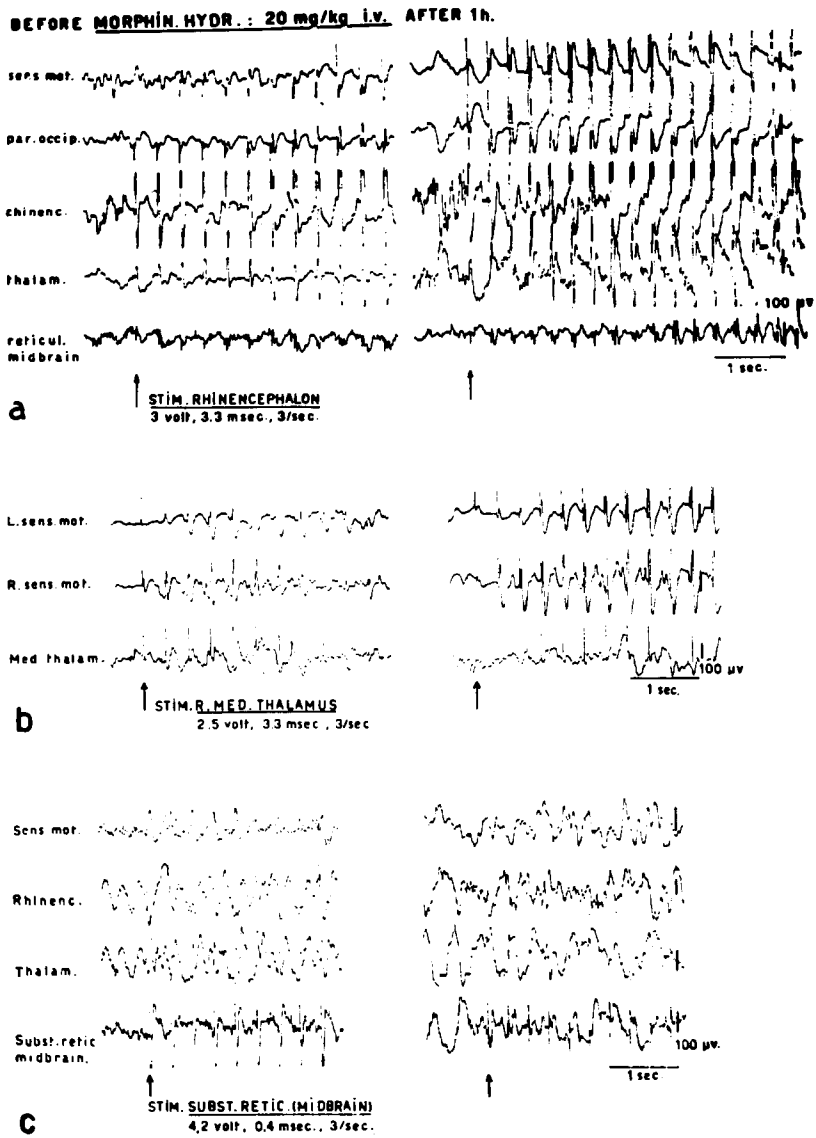

Fig. 11. Increased discharge during stimulation of rhinencephalon (a) and medial thalamus (b). Suppression of the spikes evoked by the stimulation of midbrain reticular formation (c), 1 hour after morphine (20 mg/kg).

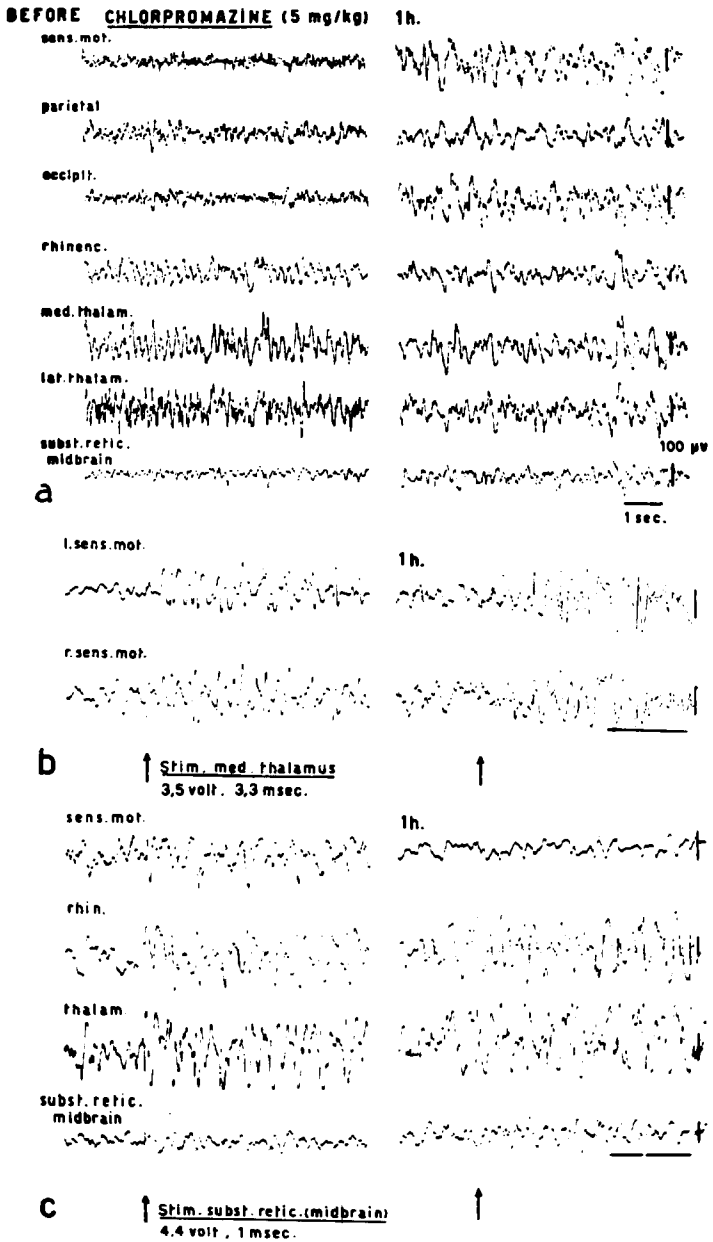

Fig. 12. (a) Sleep-like pattern, 1 hour after injection of chlorpromazine (5 mg/kg); (b) increased recruited response in the cortex to stimulation of medial thalamus; (c) slight depression of the spikes response to stimulation of midbrain reticular formation.

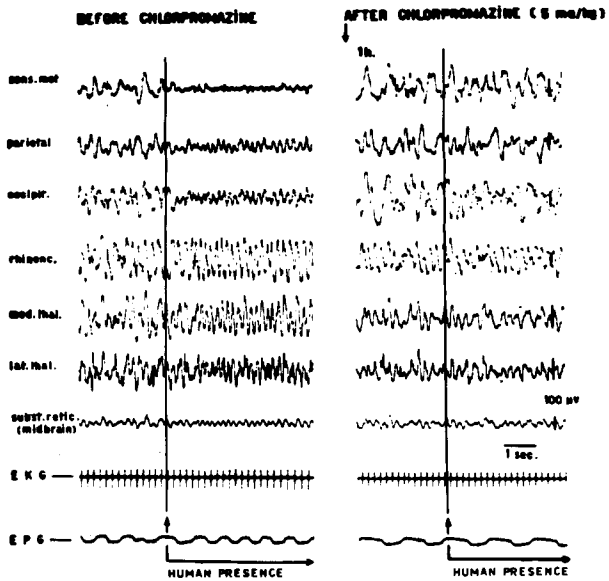

Fig. 13. Suppression of the attention reaction to human presence, 1 hour after injection of chlorpromazine (5 mg/kg).

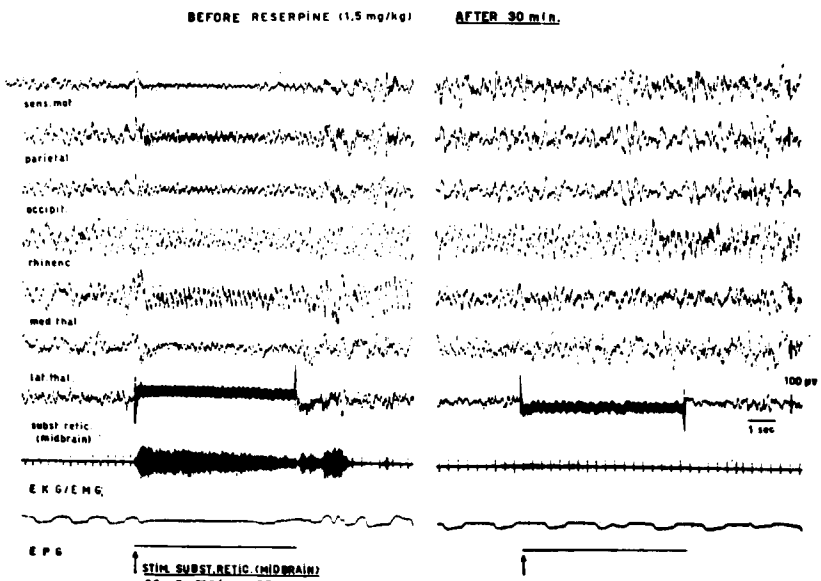

Fig. 14. Suppression of the arousal reaction to stimulation of midbrain reticular formation 30 min after injection of reserpine (1.5 mg/kg).

thalamus is depressed. The reticular system is not depressed at the midbrain level (sometimes even enhanced), but impulses ascending from this system fail to activate the cortex, since the thalamo-cortical excitability is depressed by the drug. This fact is confirmed by the raised threshold of the after-discharge (Fig. 15b, c).

The excitability of the rhinencephalon itself is not decreased, but the propagation of the rhinencephalic spikes to the cortex is often depressed (threshold of after-discharge not increased); this may contribute to tranquillization of the emotional behaviour, without impairing the consciousness (Fig. 15a).

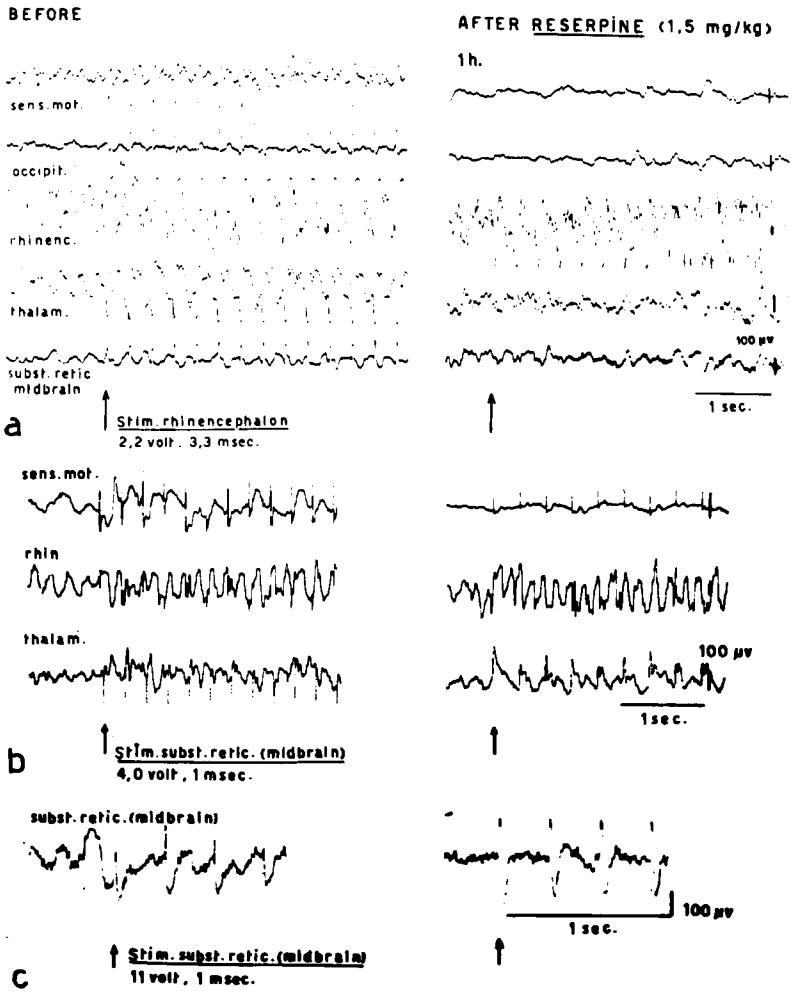

Fig. 15. Depression of the rhinencephalic spikes, after injection of reserpine (1.5 mg/kg) (a). Depression of the thalamo-cortical system which no longer responds to ascending reticular impulses.

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From this electrographic analysis, we may conclude that real tranquillizers like reserpine do not depress markedly the reticular system, at least not at the midbrain level, whereas they depress the thalamic and the cortical levels, especially the latter. The tranquillization effect may be due to a decreased propagation of the reticular and rhinencephalic impulses toward the cortex. The absence of sleep or impaired consciousness is perhaps related to a moderation of the medial thalamic system without depression of the reticular system at midbrain level.

5. *Hypnotics and sedatives*

Phenobarbital in moderate (30–50 mg kg) and strong doses (100 mg kg) induces sleep with bradypnea and shows a typical electrographic sleep pattern. After a transitory activation, it moderates the recruiting action of the thalamic intralaminary system on the thalamus and cortex, and raises the threshold of the after-discharge in these structures. Furthermore, it depresses the midbrain reticular system and the propagation of its ascending impulses. Finally, it depresses the rhinencephalic spikes.

Phenobarbital in low sedative doses (20–50 mg kg i.v.), which do not alter wakefulness, has the same effects, except in the reticular formation, which is not at all depressed at the midbrain level, and sometimes even enhanced.

From these facts, we may conclude that the sedative action of phenobarbital is associated with a moderation of the thalamic and rhinencephalic system, whereas the reticular system is not depressed at midbrain level; its ascending impulses to the thalamus and cortex are decreased, however. The sleep action of phenobarbital is accompanied by a depression of the medial thalamus and rhinencephalon (after a transitory activation), as well as of the cortex and reticular system.

Here again hypnotic action occurs with a decreased excitability of the reticular system at midbrain level and with a stronger decrease of its ascending impulses toward thalamus, rhinencephalon and cortex. In the more sedative states, there is no decreased activity of the reticular system. The stronger and irreversible hypnotic action of phenobarbital as opposed to that of morphine or chlorpromazine is perhaps related to the fact that the medial thalamic intralaminary system is also depressed.

DISCUSSION

Our experiments with drugs acting more or less specifically on autonomic brain stem centres suggest a functional interaction between the midbrain reticular system and the thalamic intralaminary system, in their relation to the cortex and consciousness. Morphine and levallorphan as typical antagonistic substances act in opposite ways on these two systems involved in the organization of consciousness and pain. Thus morphine activates the thalamic intralaminary system, in doses which depress consciousness and pain, whereas levallorphan, in doses necessary to antagonize the morphine analgesia, activates the reticular formation at the midbrain level.

Similarly the two groups of drugs have an opposite action on the rhinencephalon (hippocampus). This system is activated by morphine and depressed by levallorphan.

On the other hand, there is a difference between analgesics and tranquillizers as regards their action on the intralaminary thalamic system and the reticular formation. Morphine enhances the recruiting activity of the intralaminary thalamus system,

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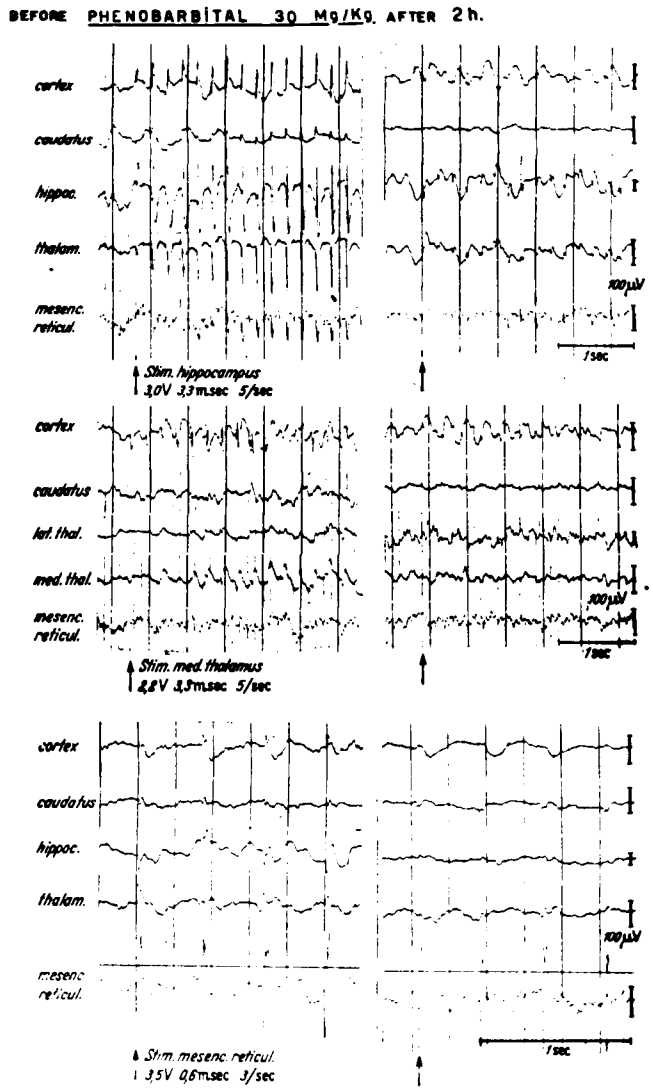

Fig. 16. Depression of discharges induced by stimulation of the rhinencephalon (hippocampus) medial thalamus, and midbrain reticular formation, 2 hours after injection of phenobarbital (30 mg kg).

whereas reserpine or serotonin depress it. Morphine depresses (and chlorpromazine depresses transitorily) the midbrain reticular system, whereas reserpine or serotonin do not depress, and sometimes even increase it at midbrain level.

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Another interesting fact is that drowsiness and the sleep-like electrographic pattern induced by morphine and chlorpromazine are associated with a general depression of the reticular activity and enhancement of the thalamic intralaminary activity. Furthermore, there is a correspondence between spontaneous electrographic symptoms ("sleep" pattern with generalized high-voltage slow waves and spindles in the sensorimotor cortex) and the symptoms evoked in the cortex by electrical stimulation of the intralaminary system (increased bilateral synchronous, recruited spikes and waves). Chlorpromazine, which increases the excitability of the intralaminary thalamus and slightly depresses the activity of the midbrain reticular system, evokes a more marked "sleep" pattern than reserpine and serotonin. These two drugs induce no sleep pattern when the thalamus is slightly depressed and when the midbrain reticular system shows a tendency to increased excitability.

These observations suggest an interaction between the activity of the midbrain reticular formation coupled with arousal and the hyperactivity of the thalamic intralaminary system, often observed in sleep.

Hypnotics like phenobarbital, in doses producing sleep abolish the interaction of these two systems; the thalamus and the reticular formation are depressed simultaneously and the cortex as well.

SUMMARY

Our investigations show that specific ergotropic or trophotropic drugs and trophotropic tranquillizers (of the chlorpromazine type) can be grouped into 2 categories according to their electrographic and functional aspects:

(a) *Ergotropic states* with decreased recruiting activity of the thalamic intralaminary system, increased or unaltered activity of the ascending reticular system and depressed activity of the rhinencephalon. Such ergotropic states are obtained mainly with cocaine, *d*-amphetamine, lysergic acid diethylamide and levallorphan, an antagonist of morphine.

(b) *Trophotropic states* (relaxation, tranquillization and sleep) with increased recruiting activity of the thalamic intralaminary system, and decreased propagation of reticular impulses to the cortex. Such states are induced by morphine, levorphan and chlorpromazine.

Reserpine, however, differs from the specific trophotropic drugs in the fact that the reticular formation is not depressed at midbrain level, whereas the thalamo-cortical levels are depressed. It shows therefore a "mixed arousal and relaxation" electrographic pattern.

The 2 aspects mentioned above cannot be distinguished when hypnotics like phenobarbitol are used in larger doses; the intralaminary thalamic system, the midbrain reticular formation and the rhinencephalon are then depressed simultaneously and their functional interaction can no longer be analyzed.

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