EFFECT OF PERIPHERAL SEROTONIN ANTAGONISTS ON CHANGES IN BACKGROUND CORTICAL ELECTRICAL ACTIVITY PRODUCED BY 5-HYDROXYTRYPTOPHAN

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5-hydroxytryptophan activates the cortex and mesencephalic reticular formation in rats. Its effect on the "cerveau isolé" preparation is reduced. Serotonin antagonists of M (morphine) and D (5-methoxytryptamine) type, and also the universal serotoninolytic drug diphenhydramine, specifically block the activation produced by 5-hydroxytryptophan.

Previous work has shown that the depriming effect of 5-hydroxytryptophan (5-HT) on conditioned defensive reflexes in rats is blocked by peripheral M- and D-antagonists of serotonin [5]. On this basis it has been suggested that the serotoninergic structures of the brain responsible for this effect of 5-HT are a special type of serotonin receptor characteristic of the central nervous system.

In the investigation described below electroencephalographic data were used to determine which of the peripheral serotonin antagonists can block the activating effect of 5-HT on cortical activity in rats.

EXPERIMENTAL METHOD

The electrocorticogram (ECoG) was recorded in rats weighing 150-200 g, with permanently implanted bipolar electrodes (diameter 150μ, stainless steel). The electrodes were introduced epidurally into the sensorimotor and visual areas of the cortex. To record potentials in the mesencephalic reticular formation and to study the effect of transection of the brain stem to obtain a "cerveau isolé" preparation, acute experiments were carried out on animals immobilized with succinylcholine (5 mg/kg, intraperitoneally), using artificial respiration. Electrodes were introduced into the mesencephalic reticular formation in accordance with coordinates given in stereotaxic atlases of the rat's brain [8, 9]. The electrical activity of the brain was recorded on a four-channel electroencephalograph of the 4ÉÉG-1 type. Serotoninergic structures of the brain were activated by means of 5-HT. The doses and methods of administration of 5-HT and the serotonin antagonists are indicated in the captions to the figures.

EXPERIMENTAL RESULTS AND DISCUSSION

Under normal conditions, on the ECoG recorded from the sensorimotor area of intact rats, low-amplitude waves with a frequency of 10-12/sec are found, alternating with periods of regular bursts of spikes, while the ECoG of the visual area consists of waves of low and medium amplitude with a frequency of 12-15/sec. From 20 to 30 min after injection of 5-HT, a definite activating effect develops, with the appearance of desynchronization in the ECoG of the sensorimotor area, and a regular high-frequency rhythm on the ECoG of the visual area. The animals' behavior showed an increase in motor activity accompanied by stereotyped actions. The activating effect of 5-HT lasted for more than 3 h.

The activating effect of 5-HT, as reflected on the ECoG of cats and rabbits, is due to excitation of serotonin receptors of the reticular formation in caudal divisions of the brain stem [6]. The analogous

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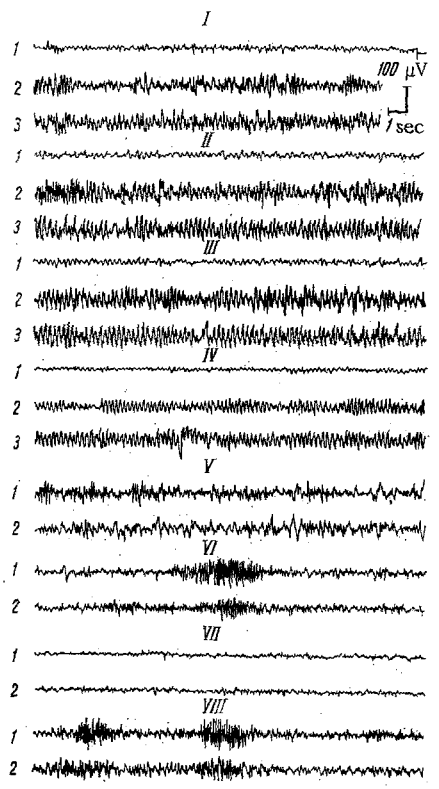

Fig. 1. Effect of 5-HT (300 mg/kg, intraperitoneally) on EEG of rats: I-IV) EEG of intact rats; I) initial background; II, III, IV) 30 min, 1 and 2 h, respectively, after administration of 5-HT; V-VIII) EEG of "cerveau isolé" preparation; V) initial background before transection; VI) after transection; VII, VIII) 40 min and 1 h, respectively, after injection of 5-HT. 1) Sensorimotor cortex; 2) visual cortex; 3) mesencephalic reticular formation.

effect of 5-HT on rats is also evidently localized in the reticular formation of the brain stem. Evidence of this is given, first, by the fact that injection of 5-HT is followed by activation of the EEG not only in the cortex, but also in the mesencephalic reticular formation (Fig. 1), and in some cases the activation arises earlier in the mesencephalic structures than in the cortex. Second, after transection of the brain at the cerveau isolé level, the activating effect of 5-HT was reduced: in some cases it failed to develop completely, and in others it persisted only for the first 30-40 min (Fig. 1).

Morphine (M-antagonist), 5-methoxytryptamine (5-MT; D-antagonist) and diphenhydramine (universal antagonist) were used as the peripheral serotonin antagonists [4].

As a preliminary step the action of serotonin antagonists themselves on the ECoG was studied. Tests showed that morphine, 5-MT, and diphenhydramine caused the appearance of slow, high-amplitude waves with periodic bursts of spikes in the sensorimotor area 20-30 min after injection. The synchronizing effect of morphine lasted for 1.5 h, and that of 5-MT and diphenhydramine for 1.5-2 h.

When these drugs were injected simultaneously with 5-HT, the activating effect of the latter was not exhibited. For example, when morphine and 5-HT were injected together, mainly high-voltage slow waves, alternating with periods of normal background activity, were recorded on the ECoG. After simultaneous injection of 5-MT and 5-HT, transient synchronization was observed, but the initial background ECoG was restored after only 15 min. At the end of the experiment (after 120 min), discrete slow discharges appeared. Roughly the same picture was observed after simultaneous injection of diphenhydramine and 5-HT (Fig. 2).

The activating effect of serotonin and 5-HT is known to take place in the reticular formation of the brain stem [6]. 5-MT is structurally very similar to serotonin. In addition, the action of 5-MT on cortical background electrical activity likewise can be localized in the brain stem, and it can therefore be postulated that the antagonism between 5-MT and 5-HT is specific in character and is localized in the region of the mesencephalic reticular formation. The depriming effect of morphine, on the basis of ECoG data, depends to some extent on excitation of the intralaminar thalamic system [1]. The synchronizing effect of diphenhydramine, which is known to possess a central cholinolytic action [7], can be attributed to the blocking of ascending activating influences at the cortical level [6]. Consequently, the antagonism between morphine and diphenhydramine, on the one hand, and 5-HT on the other, may take place, not in the reticular formation, but at higher levels of the brain, and it may be functional in character. However, the possibility cannot be ruled out that interaction between these drugs and 5-HT can also take place in the mesencephalic reticular formation because morphine and the central cholinolytics are known to exhibit their effects on this part of the central nervous system also [2].

To examine the character of the antagonism between 5-HT, morphine, 5-MT, and diphenhydramine, the effect of sodium amytal on the activating effect of 5-HT and on interaction between serotonin antagonists and adrenomimetics and cholinomimetics (amphetamine and galanthamine) was investigated. Sodium amytal, amphetamine, and galanthamine were chosen because their action on the ECoG is effected mainly through changes in the excitability of nonspecific systems of the brain stem, i.e., the same structures which are responsible for the effect of 5-HT [1, 2, 6].

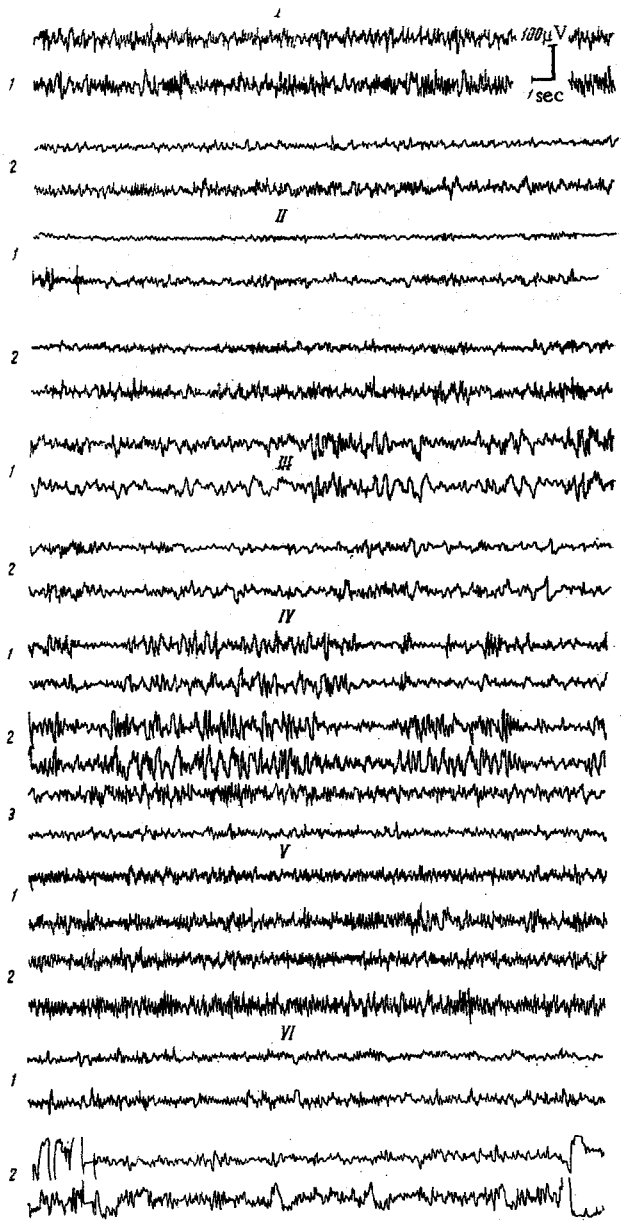

Fig. 2. Effect of 5-HT (300 mg/kg, intraperitoneally) on background EEG of sensorimotor (above) and visual (below) cortical areas of rats before and after administration of serotonin antagonists and sodium amytal. From I to VI inclusive: 1) initial background EEG; I: 2) EEG 60 min after injection of 5-HT (300 mg/kg, intraperitoneally); II: 2) EEG 60 min after injection of sodium amytal (25 mg/kg, intraperitoneally); III: 2) EEG 60 min after simultaneous injection of 5-HT and sodium amytal; IV: 2) EEG 30 min after simultaneous injection of 5-HT and morphine (2 mg/kg, intravenously); 3) EEG 60 min after simultaneous injection of 5-HT and morphine; V: 2) EEG 60 min after simultaneous injection of 5-HT and 5-MT (5 mg/kg, intravenously); VI: 2) EEG 60 min after simultaneous injection of 5-HT and diphenhydramine (30 mg/kg, intraperitoneally).

After injection of sodium amytal (25 mg/kg, intraperitoneally), slow, high-amplitude waves alternating with bursts of spikes appeared on the ECoG. The effect of the drug developed after 20-30 min and lasted for 1.5-2 h. Sodium amytal thus has an action similar to the effects of morphine, 5-MT, and diphenhydramine. Unlike the serotonin antagonists, however, this drug does not block the activating effect of 5-HT on the ECoG.

Starting from 30 min after their intraperitoneal injection, amphetamine (5 mg/kg) and galanthamine (6 mg/kg) produced definite desynchronization which lasted for at least 3 h. Central serotonin antagonists did not prevent the activating effect of these drugs. Consequently, in the doses tested, diphenhydramine, morphine, and 5-MT do not block the cholinergic and adrenergic systems of the rat brain stem.

The results of the experiments with sodium amytal, amphetamine, and galanthamine suggest that the antagonism between morphine, 5-MT, diphenhydramine, and 5-HT is specific in character and is localized, possibly, in the mesencephalic reticular formation, i.e., in the place where the effect of 5-HT is produced.

Activation induced by 5-HT was blocked by M-, D-, and universal antagonists of serotonin. The structures responsible for the activating effect of 5-HT on the ECoG are thus similar in their sensitivity to blocking agents to the serotoninergic structures through which 5-HT exerts its action on conditioned defensive reflexes, and they are evidently a special type of universal serotoninergic receptor characteristic of the central nervous system.

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