ACTION OF CATECHOLAMINES (PIPRADROL AND AMPHETAMINE) ON SOME CORTICAL SYNAPTIC SYSTEMS

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After the stimulant action of catecholamines on the mesencephalic reticular formation had been conclusively proved experimentally [2, 4, 6, 8, 17, 18], the hypothesis was naturally put forward that changes in excitability of the cerebral cortex found after administration of monoamines [7, 12, 13, 15, 16] are due to ascending influences from the brain stem. Proof that this hypothesis was correct was given by the fact that the experiments in which adrenalin and noradrenalin were directly applied to the exposed cortex were carried out with concentrations of these substances which were too high to allow any physiological significance to be attached to the excitatory effect thus produced [14].

More recently new data have been obtained, showing that nerve fibers containing monoamines are widespread in different parts of the brain, including the neocortex of the cerebral hemispheres [9].

The present investigation was accordingly carried out to determine the direct influence of adrenergic substances on the transcallosal potential (TCP) and the direct cortical response (DCR). These responses give information on changes in relatively precisely established synaptic and neuronal systems of the cerebral cortex. As adrenergic substances, pipradrol and amphetamine were used, drugs similar in their structure and central action to adrenalin and noradrenalin, but at the same time passing readily through the blood-brain barrier. Chlorpromazine was used to block adrenergic receptors. The direct action of these substances on the TCP and DCR was compared with their action through the brain stem and also with the effect of excitation of the reticular formation of the brain stem by electric current or by nociceptive stimulation.

EXPERIMENTAL METHOD

Experiments were carried out on 25 rabbits immobilized with flaxedil and maintained on artificial respiration. The animals were prepared for the experiment under other anesthesia. The cortex was covered with warm mineral oil. The points of fixation of the animal's head in the halter of the stereotaxic apparatus and the wound surfaces were anesthetized with procaine. To record the ECoG, three pairs of silver chloride wick electrodes were placed symmetrically on both hemispheres in the sensorimotor, anterior parietal, and visual regions. The TCP and DCR were recorded from the parietal cortex. The symmetrical point of the cortex of the opposite hemisphere was stimulated by single submaximal stimuli 0.5 msec in duration. The DCR were recorded at a distance of 3 mm from the stimulating electrodes when stimuli 0.1 msec in duration and slightly above threshold strength were used. Stimulation of the mesencephalic reticular formation was carried out through bipolar platinum electrodes, introduced relative to stereotaxic coordinates, using rectangular pulses of current 0.1 msec in duration and at a frequency of 200 per second. A rectangular pulse generator with radio-frequency output was used for stimulation. The potentials were recorded on a cathode-ray oscillograph with parallel recording of the ECoG on an "Al'var" 8-channel ink-writing encephalograph.

EXPERIMENTAL RESULTS

Intravenous injection of pipradrol or amphetamine (3-5 mg/kg) led after 1-3 min to a persistent decrease in the amplitude of the DCR and TCP (Fig. 1). The decrease in DCR and in the surface-negative component of the TCP reached, on the average, 50% of their initial value, whereas the mean value of the surface-positive component of the TCP was 80% of normal. A clear parallel was observed between the appear-

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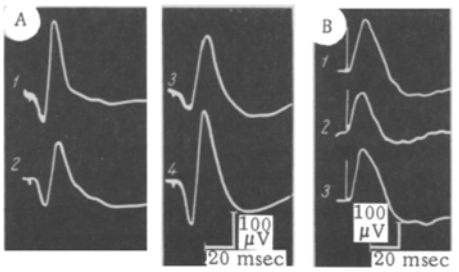

Fig. 1. Changes in TCP (A) and DCR (B) during intravenous injection of pipradrol, followed by chlorpromazine. On all curves negativity beneath the active electrode is shown by an upward deflection of the beam; the moment of stimulation is shown by an artefact. A: 1) Control; 2) 10 min after injection of pipradrol (3 mg/kg); 3) 4 min; 4) 15 min after injection of chlorpromazine (4 mg/kg); B: 1) control; 2) 5 min after injection of pipradrol (3 mg/kg); 3) 8 min after injection of chlorpromazine (4 mg/kg).

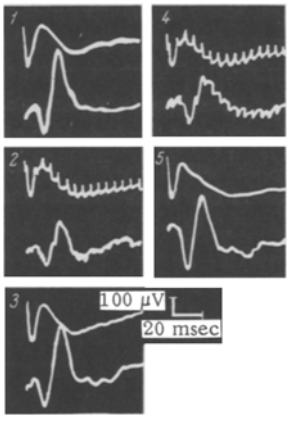

Fig. 2. Effect of direct stimulation of reticular formation on TCP and DCR and action of chlorpromazine. Simultaneous recording of DCR (top curve) and TCP (bottom curve); 1) control; 2) stimulation of reticular formation; 3) 8 min after intravenous injection of chlorpromazine (4 mg/kg); 4) stimulation of reticular formation against the background of the action of chlorpromazine; 5) 3 min after end of stimulation.

ance of ECoG activation and reduction of the DCR and TCP. Similar changes in DCR and TCP were observed during direct stimulation of the mesencephalic reticular formation, pricking the paw with a needle, and stimulation of the sciatic nerve.

The adrenolytic drug chlorpromazine, when injected systemically (4 μg/kg), clearly blocked the changes described above in cortical excitation after 5-10 min: the DCR and TCP, when reduced by the action of pipradrol or amphetamine, were restored to their initial level. Meanwhile chlorpromazine caused the picture of ECoG activation to disappear—a high-amplitude slow activity with "spindles", characteristic of the resting state, appeared [1, 3, 10]. In the above dose, chlorpromazine had no effect on the DCR and TCP if these were not modified by preceding administration of catecholamines.

Reduction of the investigated potentials and ECoG activation during direct stimulation of the mesencephalic reticular formation was not removed by the action of chlorpromazine (Fig. 2). Hence, chlorpromazine does not depress the transmission of reticular influences in the cortical link or it affects them much more weakly. Consequently, under the direct action of catecholamines, depression of the cortical

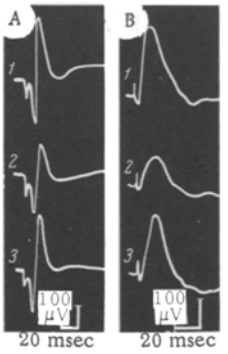

Fig. 3

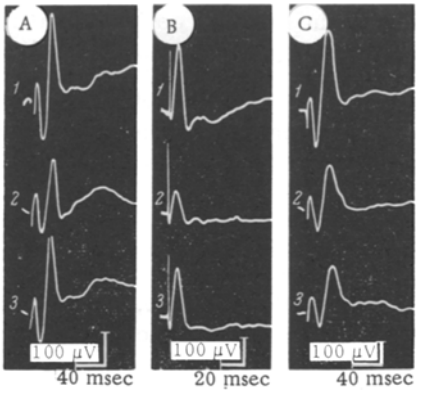

Fig. 4

Fig. 3. Changes in TCP (A) and DCR (B) after intravenous injection of pipradrol, followed by chlorpromazine. A: 1) Control; 2) 5 min after injection of pipradrol (3 mg/kg); 3) 10 min after injection of benactyzine (1 mg/kg); B: 1) control; 2) 9 min after injection of pipradrol (3 mg/kg); 3) 10 min after injection of benactyzine (1 mg/kg).

Fig. 4. Effect of local application of pipradrol to the cortex on TCP and DCR and effect of subsequent intravenous injection of chlorpromazine (A and B) and benactyzine(C). A: 1) Control (application of physiological saline); 2) 4 min after application of 1% pipradrol solution; 3) 7 min after injection of chlorpromazine (4 mg/kg); B: 1) control (application of physiological saline); 2) 3.5 min after application of 1% pipradrol solution 3) 6 min after injection of chlorpromazine (4 mg/kg); C: 1) control (application of physiological saline); 2) 5 min after application of 1% pipradrol solution; 3) 10 min after injection of benactyzine.

potentials of the TCP and DCR is associated with ascending influences of the mesencephalic reticular formation, and judging from data obtained previously in the authors' laboratory [5], the final cortical link of this pathway is cholinergic. In fact, the muscarine-like cholinolytic drug benactyzine hydrochloride, when injected intravenously in the present experiments, completely restored the TCP and DCR to their initial level after reduction by pipradrol or amphetamine, and at the same time blocked activation of the ECoG (Fig. 3). The nicotine-like cholinolytic drug gangleron, when injected into the general circulation, had no such action, in full agreement with observations indicating that the mechanism of the activation reaction during stimulation of the reticular formation is purely muscarine in nature.

The direct action of pipradrol on the cortex was investigated by application of a 1% solution to the surface of the cortex. In the experiments described, depression of the TCP and DCR was observed. However, the effect of subsequent injection of adrenolytics or cholinolytics on these modified potentials differed. After systemic administration of chlorpromazine an increase in the previously reduced TCP and DCR was observed, amounting in some cases to restoration of their normal value (Fig. 4, A and B). Conversely, intravenous injection of benactyzine had no essential action on the TCP when reduced by pipradrol (Fig. 4,C).

The results described above confirm that adrenergic substances, when administered systemically, influence cortical excitation mainly through the reticular structures of the mesencephalon. This action of the adrenomimetics is abolished by the central adrenolytic chlorpromazine, and the block takes place at the level of the brain stem. The adrenomimetic effects could also be blocked at the cortical level by benactyzine, confirming the muscarine-like cholinergic nature of the final link of reticulo-cortical activation.

Experiments in which pipradrol was applied to the surface of the cortex revealed that adrenergic structures are present in these neuronal systems associated with the origin of the transcallosal potential, and also with the reaction of the surface neuropil, i. e., with the direct cortical response. The specific character of this effect is shown by its abolition by the central adrenolytic chlorpromazine. Depression of the TCP and DCR by the direct action of pipradrol on the cortex evidently reflects depression of the synaptic transmission of excitation and depends on a decrease of excitability of the postsynaptic membrane of the cortical neurons. It has in fact been shown by Krnjević and Phillis [11] that electrophoretic admin-

istration of catecholamines to the cortical neurons causes depression of synaptic transmission and also depression of spontaneous discharges of neurons and their responses to glutamate.

It thus follows that the adrenergic synaptic systems at the level of the mesencephalic reticular formation are excited by catecholamines, while those in the cortex are depressed. When adrenomimetics act through the blood stream this direct effect cannot be found, for it is masked by activating influences of the reticular formation.

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