EFFECT OF GENERAL ANESTHETICS AND PSYCHOTROPIC DRUGS ON CONVERGENCE OF EXCITATION OF CORTICAL UNITS

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Convergence of excitation on 350 units of the somatosensory cortex was studied in acute experiments on rabbits against the background of pharmacological action. A considerable decrease in the number of polysensory neurons was found during the action of substances disturbing cortical integrative processes (urethane, nembutal, benactyzine hydrochloride). The action of each of these substances is characterized by definite changes in the relative numbers of mono- and polysensory neurons, and these were found to be a more specific criterion than EEG changes.

It is generally accepted that goal-directed behavior in animals and man is based on the integrative activity of the brain. To understand the mechanism of action of general anesthetics and psychotropic drugs which modify behavior, it is essential to have information on the effect of these drugs on integrative processes in the central nervous system.

According to the concept of a functional system and the convergence theory of conditioning [4], the convergence of different forms of excitation onto a single unit play a special role in integrative processes.

Although general anesthetics and psychotropic drugs primarily block subcortical sources of activating influences, the aftereffects of this block produce considerable modification of cortical activity [2, 7, 9, 11, 12]. It is these changes in cortical integrative processes which are most closely related to disturbances of goal-directed behavior.

The object of this investigation was to investigate the extent to which the basis of integration (convergence of different forms of excitation on cortical units) is disturbed following administration of widely known psychopharmacological agents (chlorpromazine and benactyzine) and general anesthetics (urethane and nembutal).

EXPERIMENTAL METHOD

Responses of 350 somatosensory cortical units to electrodermal and visual stimulation were studied in 40 acute experiments on adult rabbits weighing 2-2.5 kg.

In experiments on unanesthetized rabbits the animals were fixed in a stereotaxic apparatus after brief inhalation of ether. Fixation of the waking rabbit in the stereotaxic apparatus was adequate for the microelectrode investigation and did not require the use of muscle relaxants. Administration of the test drugs and recording of unit activity began 2-2.5 h after the completion of all preliminary manipulations.

The microelectrodes consisted of glass micropipets with a tip 1-2 μ in diameter, filled with 3 M NaCl solution, and recordings were made from the focus of maximal activity of the evoked potential to electrodermal stimulation of the contralateral hind limb.

Integral electrical activity of the somatosensory cortex was recorded simultaneously with unit activity.

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Electrodermal stimulation ("Fisiovar" stimulator) was applied as a series of 10 pulses, from 10 to 40 V in amplitude, in the course of 1 sec.

Photic stimulation consisted of flashes from a "Soneclat" photophonostimulator, which were applied at a frequency of 10/sec also for 1 sec.

Unit activity, the EEG, and markers of stimulation and time were recorded by means of the Alvar "Biophase" complex.

EXPERIMENTAL RESULTS

The experiments of series I (control) were performed on 13 waking rabbits. In these experiments, the integral electrical activity characteristic of the waking state was recorded in the somatosensory cortex, and after electrodermal stimulation this was replaced by a well-marked EEG arousal reaction. Flashes usually did not evoke such a response.

Of 100 investigated units of the somatosensory cortex, 48% responded to none of the presented stimuli, 18% responded only to electrodermal stimulation (2% by a decrease, 16% by an increase in frequency), and 6% responded only to photic stimulation; 28% were polysensory and responded both to electrical and to photic stimulation.

In the experiments of series II, conducted on 6 rabbits under urethane anesthesia (2 g/kg, intraperitoneally), 50 units of the somatosensory cortex were studied. The number of nonresponding neurons was increased to 82% ($P < 0.005$). As in the control group, 18% of units responded to electrodermal stimulation (2% by a decrease, 16% by an increase in frequency). No polysensory neurons or neurons responding to photic stimulation could be found.

In these experiments, just as in those described by other workers [1, 16, 19], urethane did not abolish the EEG arousal reaction in response to electrodermal stimulation.

Under nembutal anesthesia (40 mg/kg, intravenously), on the other hand, spindles typical of barbiturate anesthesia were observed on the EEG. The desynchronization reaction to electrodermal stimulation was absent.

Of 50 units recorded in experiments on 5 rabbits under nembutal anesthesia, 62% did not respond, 28% responded (12% by a decrease, 16% by an increase in frequency) to electrodermal stimulation (an increase of 10%; $P < 0.05$), and 10% responded to both types of stimulation (a decrease of 18%; $P < 0.005$). No neurons responding to photic stimulation only could be found.

In the experiments of series III, conducted on 11 rabbits, the effect of chlorpromazine (8-10 mg/kg, intramuscularly), a representative of the major tranquilizers, was studied. The criterion of the effectiveness of its action on the central nervous system was the existence of typical changes in the EEG: the appearance of slow waves in the somatosensory cortex and weakening or absence of the arousal reaction in response to electrodermal stimulation.

However, despite clear changes in the EEG, no changes were found in the ability of the cortical units to respond to these stimuli. Almost exactly as in the control experiments, of 100 units recorded 14% responded only to electrical stimulation (4% by a decrease, 10% by an increase in frequency; $P = 0.75$), 4% responded to photic stimulation ($P = 0.9$), 30% were polysensory and responded to both stimuli, and 52% did not respond to either ($P = 0.9$).

In the experiments of series IV, conducted on 5 rabbits, a minor tranquilizer, benactyzine hydrochloride, was used in a dose of 5 mg/kg, intramuscularly.

Following administration of benactyzine, the number of polysensory neurons showed a sharp decrease to 8% ($P < 0.005$), whereas the number of monosensory neurons remained unchanged: 20% responded to electrical stimulation (or by a decrease in frequency), and 6% to photic stimulation.

Just as during the action of chlorpromazine, slow waves were observed on the EEG. Electrodermal stimulation did not evoke a desynchronization reaction.

These results show that a change in the number of polysensory neurons in the cortex is a good criterion of the degree of disturbance of integrative processes in the brain. General anesthetics, for instance,

during whose action goal-directed behavior is impossible, produce considerable weakening or total abolition of convergence of excitation on cortical neurons. Tranquilizers such as chlorpromazine, on the other hand, which do not produce marked disintegration, but simply abolish certain components, mainly motivational [1, 15, 18], from afferent synthesis, do not change the number of polysensory cortical neurons.

At the same time, these results very demonstratively confirm the view that various pharmacological agents act specifically on subcortical activating structures [2, 12]. Urethane, for example, which blocks certain subcortical structures, leaves only monosensory neurons functioning in the somatosensory cortex and abolishes responses of polysensory neurons to both stimuli. Nembutal, on the other hand, which blocks other subcortical structures, reduces the number of polysensory neurons mainly by depressing their response to photic stimulation. This can actually lead to a slight increase in the number of polysensory units. During the action of benactyzine, the number of polysensory cells is reduced, but neurons responding only to photic stimulation, which is inadequate relative to the somatosensory cortex, continue to function.

The specific distribution of groups of cortical units during the action of various pharmacological agents demonstrates that: "Every pharmacological agent of narcotic or tranquilizing character produces fractional dissociation in subcortical nuclei, allowing some influences from the cortex to pass and, on the other hand, blocking other influences" [3].

The "neuron formula" reflects the specific nature of the action of various drugs more closely than the evoked potential [6, 12, 13] or the integral EEG [9, 11]. In the present experiments, just as in those described by other workers [8, 10, 14], both nembutal and chlorpromazine abolished the EEG arousal reaction to electrodermal stimulation. Under these circumstances the "neuron formula" shows that nembutal disturbs convergence while chlorpromazine does not. In the waking state, an arousal reaction was observed under urethane anesthesia also, whereas the "neuron formula" shows that urethane produces much greater disturbance of convergence than, for example, chlorpromazine which abolishes the EEG arousal reaction.

During analysis of the results obtained by administration of chlorpromazine and benactyzine, the fact was noted that the major tranquilizer (chlorpromazine) does not prevent cortical neurons from receiving stimuli of a different sensory modality, whereas the minor tranquilizer (benactyzine) considerably reduces the number of polysensory neurons. These findings agree with the discovery that benactyzine inhibits such a predominantly cortical function as extrapolation, which is not disturbed by chlorpromazine, even in toxic doses [17]. The model point in the mechanism of action of chlorpromazine on the central nervous system is known to be its inhibitory action on the reticular formation which, according to Vogt [21], contains the largest number of adrenergic structures, whereas the lowest concentrations of adrenalin and noradrenalin are found in the cerebral cortex [1, 2, 5, 8]. The work of Prozorovskii [13], Krnjevic [20], and Turenko [16] has demonstrated the existence of a large number of cholinergic structures in the cerebral cortex and their sensitivity to benactyzine and other cholinolytics. Benactyzine, if applied locally to the cortex, abolishes the desynchronization reaction in response to peripheral stimulation [15, 16], whereas chloropromazine produces the same effect only if administered generally or if applied locally to the reticular formation [5, 8]. It can therefore be postulated that the greater disturbance of cortical convergence during the action of benactyzine was partly due to its direct action on cortical neurons (on synapses).

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