EFFECT OF INHIBITORS OF CATECHOLAMINE SYNTHESIS (α-METHYLTYROSINE AND DISULFIRAM) ON SPONTANEOUS UNIT ACTIVITY OF THE SENSOMOTOR CORTEX AND RESPONSES TO AFFERENT, CAUDATE, AND RETICULAR STIMULATION

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Spontaneous activity of single units of the sensomotor cortex and their responses to flashes, clicks, electrical stimulation of the skin, and stimulation of the caudate nucleus and mesencephalic reticular formation were recorded in unanesthetized, curarized cats. α-Methyltyrosine (150 mg/kg) and disulfiram (400 mg/kg), injected 6 h before the experiment, caused an increase in the grouping of the spontaneous activity, an increase in the number of spontaneously active units, and an increase in the amplitude of the afferent short-latency responses. Phasic and tonic inhibition of the neurons during low-frequency stimulation of the caudate nucleus was potentiated by α-methyltyrosine, but weakened by disulfiram. Against the background of the action of the first of these agents, amphetamine did not exhibit its blocking action on caudate inhibition. Both substances weakened facilitatory and inhibitory reticular influences, and disulfiram was more effective in this respect.

KEY WORDS: inhibitors of catecholamine synthesis; cortical unit activity.

Previous experiments have shown that α-methyltyrosine (α-MT), a compound which blocks the initial stage of catecholamine synthesis [10, 16], potentiates the behavioral manifestations of the inhibitory function of the caudate nucleus [3]. Disulfiram (DS), which selectively disturbs the conversion of dopamine into noradrenalin [8, 14], has no such action.

Since the character of the cell processes accompanying this phenomenon has not been explained, the effect of inhibitors of catecholamine synthesis on the spontaneous activity of single sensomotor cortical neurons and their evoked responses to stimulation of the caudate nucleus was studied. Meanwhile the responses of the cells to afferent and reticular stimulation were compared.

EXPERIMENTAL METHOD

Experiments were carried out on unanesthetized, immobilized cats. As a first step bipolar stimulating electrodes were inserted stereotaxically into the head of the caudate nucleus and into the mesencephalic reticular formation of the animals. A few days later the thresholds of the animals' behaviorial responses to stimulation of the brain were determined and intraperitoneal injections given of α-MT (Hoffman–LaRoche) in a dose of 150 mg/kg or DS (the commercial preparation Teturam) in a dose of 400 mg/kg. After a delay of 6 h and where the thresholds of the behavioral responses had been verified, unit activity of the sensomotor cortex was recorded in an acute experiment [1]. The recording continued for 7-8 h. Besides the spontaneous activity, the intensity of the unit responses to afferent (flashes, clicks, electric shocks to the skin) and cerebral stimulation was estimated quantitatively. The indices of inhibition

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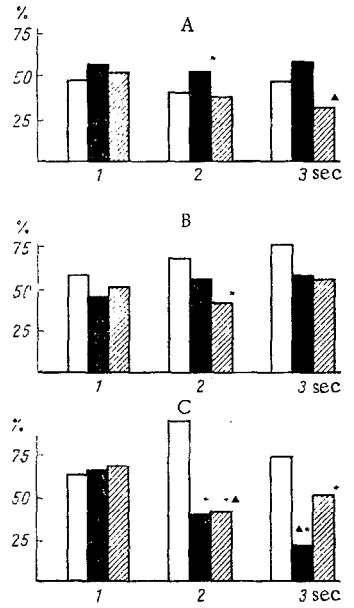

Fig. 1

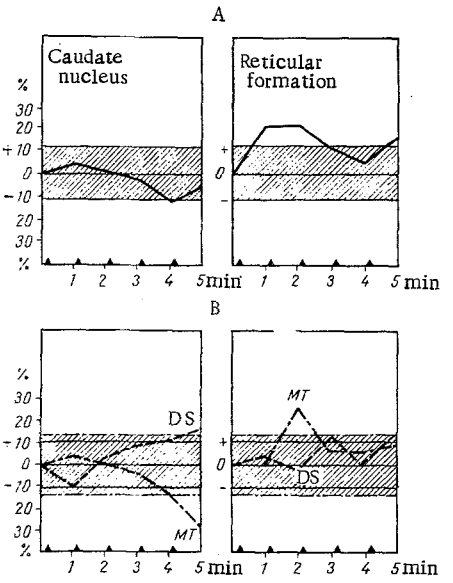

Fig. 2

Fig. 1. Changes in intensity of caudate and reticular responses of cortical cells during stimulation of the brain for 3 sec and after administration of α-MT and DS. A) Caudate inhibition; B) inhibition during stimulation of reticular structures; C) reticular facilitation. Unshaded columns – normal; black columns – after administration of α-MT; obliquely shaded columns – after DS. A statistically significant shift ($P < 0.05$) compared with the control values after stimulation for 1 sec is marked by an asterisk; a triangle denotes the same for the effect of the substance after 1 sec. Abscissa, time from beginning of stimulation (in sec); ordinate, intensity of response (in %).

Fig. 2. Effect of α-MT and DS on tonic changes in spontaneous cortical unit activity during repeated stimulation of caudate nucleus and reticular formation. A) normal; B) after injection of compound. Arrows indicate periods of brain stimulation. Obliquely shaded region represents confidence limits of mean spontaneous firing rate. On the bottom graphs it is bounded by a continuous line for DS and a broken line for α-MT. Abscissa, time (in min); ordinate, changes (in %) in spontaneous firing rate during brain stimulation in the direction of an increase (+) or decrease (–) relative to the initial level (taken as 0).

or facilitation were determined by the formula $(n-e)/e$, where n is the mean discharge frequency per second at the time of stimulation, and e the frequency before stimulation.

EXPERIMENTAL RESULTS

The behavior of 51 sensomotor neurons was studied after administration of α-MT and of 58 sensomotor neurons after administration of DS. The patterns of their spontaneous and evoked activity were compared with the activity of more than 100 neurons in animals receiving neither compound.

Spontaneous Activity and Responses to Afferent Stimulation. Both inhibitors increased the spontaneous firing rate of the cortical neurons very slightly. Normally it was 14 impulses/sec and after administration of α-MT and DS it rose to 17 and 15 impulses/sec, respectively. At the same time there was a distinct change in the character of the discharges, which were of the grouped or volley type five times more often than normally (30% compared with 6%).

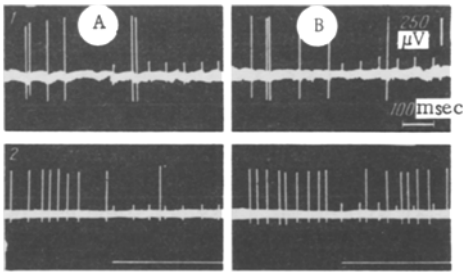

Fig. 3. Effect of amphetamine on caudate inhibition of sensomotor units after administration of α-MT (1) and DS (2): A) before; B) after injection of 2 mg/kg amphetamine.

Another feature of the action of α-MT and DS was an increase in the number of spontaneously active cortical neurons. After insertion of the microelectrode perpendicular into the surface of the posterior sigmoid gyrus (in somatosensory area III) to a depth of 6 mm, it could have penetrated also into the subjacent gyrus, and in so doing it would have recorded the activity of three cortical areas in the same track. This corresponds to penetration of zones III, IV, and VI (using Hassler's classification [12]). In intact animals along the whole length of this track an average of 23 cells was found (data for five consecutive tracks). After administration of the inhibitors the number of spontaneously active cells found averaged 30 for α-MT and 33 for DS ($P < 0.05$).

The structure of the response of the neurons (the number of cases of inhibition, of activation, and of no change in the spontaneous firing rate) to afferent stimulation showed no significant change. The number of long-latency responses (latent period 40-150 msec) of tonic type fell under the influence of α-MT (43%, normal 52%; $P < 0.05$), but under the influence of DS it rose slightly (58%). In addition, α-MT appreciably increased the percentage of tonic responses of inhibitory character. Under the influence of the inhibitors short-latency responses (10-40 msec) to heteromodal stimuli increased significantly more often. For instance, after administration of α-MT stable discharges to accoustic and visual stimuli were recorded in 16%, compared with 10% after DS. Their number in the control, however, did not exceed 3.5%.

Responses to Stimulation of the Caudate Nucleus. In accordance with previous observations, the threshold of the behavioral delay of movements in response to low-frequency (2-10 impulses/sec) stimulation of the head of the caudate nucleus was lowered by α-MT but unchanged by DS. Analysis of the response structure of the sensomotor neurons to stimulation of the caudate nucleus with a frequency of 10 impulses/sec and with a current of threshold strength for the delay response showed that it was unchanged by α-MT. Meanwhile DS reduced the number of inhibitory responses, as a result of which the percentage of reactive cells increased (in the control the two types of responses numbered 54 and 19%, after DS 37 and 44%, respectively).

Neither substance changed the intensity of caudate inhibition as an on-response (first second of recording). However, later α-MT gradually strengthened the inhibition, and during the 2nd second this change became statistically significant (Fig. 1). After injection of DS the inhibitory effect during the first 2 sec of stimulation effect was close to the control level, but after 3 sec the depression of the discharge was much weaker. When this method was used to assess the phasic inhibitory response, α-MT was thus seen to potentiate, while DS, on the other hand, weakened caudate inhibition.

This conclusion was confirmed by analysis of the character of the tonic influences of the caudate nucleus on cortical unit activity. Periodic brief tetanization of the brain (for 5 sec per min for 5 min) caused the mean spontaneous firing rate to fall gradually, although not outside the limits of variation of single unit activity (Fig. 2). α-MT and DS had directly opposite effects on the tonic changes of spontaneous activity of this type. Whereas α-MT emphasized still more the normal tendency, making the shift significant at the fifth minute of recording, DS, on the other hand, significantly increased the firing rate.

The potentiation of the phasic and tonic inhibitory influences of the caudate nucleus on the neocortical cells by the action of α-MT and the absence of any such properties of DS thus confirm the results of the behavioral experiments. This fact can be regarded as a consequence of the disturbance of catecholamine synthesis by α-MT and, in particular, a decrease in the level of striatal dopamine, followed by the liberation of the inhibitory mechanisms of the nucleus from under the retraining control of the substantia nigra [6, 7, 15]. While selectively disturbing the formation of noradrenalin and bringing about an accumulation of striatal dopamine [9, 11], DS evidently did not change or increase the integral striatal delay.

Indirect proof of the role of nigro-striatal dopaminergic mechanisms in the action of α-MT and DS is provided by the results of the experiments with amphetamine. Amphetamine is known to mobilize nigro-striatal synapses and to weaken the inhibition of cortical neurons during stimulation of the caudate nucleus [2, 5, 15]. After administration of α-MT, amphetamine (2-3 mg/kg, intravenously) did not disturb caudate inhibition of the sensomotor units, but in combination with DS it depressed it slightly (Fig. 3).

Responses to Stimulation of the Reticular Formation. Brief stimulation (at 50 impulses/sec for 10 sec) of the mesencephalic reticular formation evoked an orienting response in the unimmobilized animals and the compounds studied had no significant effect on the threshold of its appearance. The cortical neurons responded to stimulation with the same parameters either by inhibition or by facilitation of the spontaneous activity. On the whole the structure of the reticular effects was unchanged. However, the intensity of individual components of the response itself was altered. Under the influence of α-MT and DS there was a similar tendency toward weakening of inhibition of discharges of reticular origin, but the change evoked by DS between 1-2 sec of stimulation was more distinct and was statistically significant. Both substances significantly weakened reticular facilitation between the 2nd and 3rd second (Fig. 1).

Tonic changes in spontaneous activity during repeated tetanization of the reticular structures were emphatically activation in character. They were weakened both by α-MT and by DS; the effect of the latter was more marked (Fig. 2).

By contrast with the caudate responses, reticular influences were consistently weakened by both substances. Facilitation of the cortical neurons was particularly severely affected. These facts explain the distinctive behavior of the spontaneous activity and afferent responses of the cells after disturbance of catecholamine synthesis. The grouping of the discharges and the increase in number of short-latency responses could be the result of primary inhibition of the ascending activating mechanisms of the brain stem [4, 13]. On the other hand, the unequal effect of α-MT on reticular and caudate inhibition is further confirmation of the ability of this compound to strengthen the inhibitory properties of the neostriatum.

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