COMPARATIVE EFFECT OF AMPHETAMINE AND CAFFEINE ON SPONTANEOUS ACTIVITY OF SENSOMOTOR CORTICAL UNITS AND THEIR RESPONSES TO STIMULATION OF THE CAUDATE NUCLEUS

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In acute experiments on anesthetized cats activity of sensomotor cortical units was recorded during low-frequency stimulation of the head of the caudate nucleus. Amphetamine (1 mg/kg), although not significantly affecting the spontaneous firing rate, increased the number of spontaneously active cortical units. Meanwhile inhibition of these units during stimulation of the caudate nucleus was weakened. Amphetamine had a stronger suppressive action on the inhibition arising from the ventro-lateral portion than from the dorso-medial portion of the head. In the case of caffeine the location of the stimulating electrodes was unimportant.

KEY WORDS: cerebral cortex; basal ganglia; drug action.

Arushanyan [1] has postulated that the psychostimulant effect may be accompanied by weakening of inhibitory control of the caudate nucleus over cortical activity. It therefore seemed interesting to compare the effect of doses of amphetamine and caffeine, adequate to produce psychostimulation, on spontaneous activity of sensomotor cortical neurons and also on their responses evoked by stimulation of the caudate nucleus.

The present investigation is a continuation of others started previously for the purpose of studying the central properties of psychostimulants [4, 6].

EXPERIMENTAL METHOD

Experiments were carried out on 52 unanesthetized cats immobilized with muscle relaxants. The technique of recording unit activity from the sensomotor area of the neocortex, of stimulating the basal ganglia, and of analyzing the results was described earlier [2, 4]. The drugs for testing were injected intravenously at a restricted speed in order to avoid fluctuations of arterial pressure. A wide range of doses was used (1-5 mg/kg for amphetamine and 10-40 mg/kg for caffeine). According to data in the literature and the results of the writers' experiments on cats, the optimal dose of amphetamine giving a definite increase in the various behavioral tests is 1 mg/kg and the analogous dose of caffeine is 15-20 mg/kg. Attention in this investigation was therefore concentrated on the effect of the above doses.

EXPERIMENTAL RESULTS

Spontaneous Activity. Over 300 neurons in the sensomotor coretx mainly in the region of the posterior sigmoid gyrus were tested: 30 of them were studied in detail before and after injection of amphetamine and 22 in the experiments with caffeine. The results showed that neither drug, in a psychostimulant dose had a significant effect on the mean spontaneous firing rate regardless of the location and functional properties

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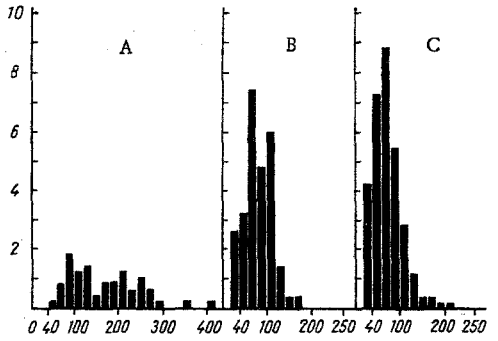

Fig. 1. Changes in histogram of consecutive interspike intervals of spontaneous activity of a sensomotor neuron under the influence of amphetamine. Ordinate, mean number of interspike intervals from five epochs (epoch of analysis 2 sec); abscissa, duration of interspike intervals (in msec). A) Initial spontaneous activity; B and C) after injection of amphetamine in doses of 1 and 2 mg/kg, respectively.

of the neurons. In both cases the rate increased very little (from 14 to 16 spikes/sec), but the difference was not significant. A statistically significant increase in frequency was observed only when the doses were doubled.

Analysis of histograms of the consecutive first-order interspike intervals showed no difference between the action of the drugs. With the cumulation of the amphetamine or caffeine, the evolution of the histograms was typical and uniform. With an increase in dose and in the frequency of the spontaneous activity they all acquired a more asymmetrical form, resembling the Poisson distribution of intervals (Fig. 1). The decrease in variability of the firing rate of the cells was accompanied by a decrease in the number of long interspike intervals and an increase in the number of short.

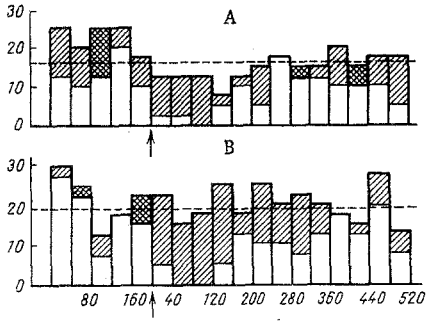

Fig. 2. Effect of amphetamine and caffeine on poststimulus histogram of sensomotor neurons in response to single stimulation of the head of the caudate nucleus. Ordinate, firing rate (spikes/sec); abscissa, time of recording unit activity (in msec). Columns show mean value of spike activity (for 10 cells in each group) before and after application of a single pulse to the caudate nucleus (moment of stimulation marked by arrow). Obliquely shaded part of column represents effect of drug in the case of an increase, and cross-hatched part represents effect in the case of a lowering of the initial firing rate. Broken line shows mean spontaneous firing rate. A) Effect of amphetamine, 1 mg/kg; B) after injection of caffeine, 20 mg/kg.

Meanwhile the psychostimulants clearly increased the percentage of spontaneously firing units. Along the length of one track through all layers of the cortex their number increased on the average (data for three tracks) by 40% for amphetamine and by 64% for caffeine. No predominant effect of the drugs on the cells in any particular cortical layer could be detected.

Responses to Stimulation of the Caudate Nucleus. In most cases the sensomotor neurons responded to low-frequency (2-10/sec) stimulation of the head of the caudate nucleus by inhibition of spike activity [3, 8, 9]. Single stimulation (1-2/sec) frequently led to a well-marked pause, usually arising immediately after the stimulus and lasting 150-200 msec. As analysis of the poststimulus histograms shows, amphetamine and caffeine clearly depressed this type of inhibitory response. Suppression not only of the late but also of the initial phase of the response was observed. Comparison of the drugs shows that amphetamine, in full agreement with earlier observations [4], is inferior to caffeine in its ability to disturb the inhibitory pause in response to stimulation of the caudate nucleus (Fig. 2). Caffeine also more frequently reverses the inhibition into facilitation.

Inhibition of unit activity during repetitive (10/sec) stimulation of the caudate nucleus also was weakened by the psychostimulants, and often inhibitory responses gave way to facilitatory. When inhibition remained, its intensity,

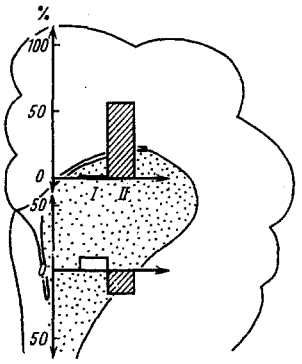

Fig. 3. Action of caffeine and amphetamine on inhibition of sensomotor neurons depending on location of stimulating electrodes in head of caudate nucleus. Ordinate, intensity (in %) of inhibition (upward columns) and facilitation (downward column). Columns on scheme of frontal section through head of caudate nucleus indicate change in intensity of inhibition evoked by stimulation of different points of the nucleus (in % of initial level) under the influence of caffeine, 20 mg/kg (I), and amphetamine, 1 mg/kg (II). Caffeine completely abolished inhibition from the dorso-medial portion whereas amphetamine, accompanied by stimulation of the ventro-lateral parts of the nucleus, led to reversal of inhibition into facilitation. Position of columns corresponds to location of electrodes.

as shown by the aggregated data, fell in a similar manner for both drugs (the index of inhibition fell from 0.47 to 0.11). A definite relationship was found: the higher the initial value of the inhibition, the weaker the action of the drugs. By increasing the strength of stimulation it was possible to restore a response suppressed by the drug. On the whole, caffeine and amphetamine gave similar changes in the ratio between the numbers of inhibitory and facilitatory responses. Whereas normally the mean number of inhibitory responses was 65%, under the influence of the drugs it fell to 40%. For this reason stimulation of the caudate nucleus was more often ineffective (the number of cases in which the cells did not respond was virtually doubled), and more responses of activation occurred (20% instead of 10%). With an increase in the dose of the drugs (amphetamine up to 2-3 mg/kg and caffeine to 30-40 mg/kg) these changes became more marked still.

By the above criteria no sharp differences could be detected in the action of amphetamine and caffeine, but nevertheless it was not completely identical. The location of the stimulating electrodes in the caudate nucleus is not always unimportant for the effect of psychostimulants. Different parts of its head are known to affect motor responses and activity of sensomotor cortical neurons differently [5, 7, 10]: inhibition is evoked more often from the ventro-lateral region than from the dorso-medial and it is stronger. Comparison of the action of the drugs with respect to responses to stimulation of the caudate nucleus and the location of the stimulating electrodes showed that caffeine abolishes responses to stimulation of all parts of the nucleus with equal success (Fig. 3). Conversely, amphetamine was characterized by definite selectivity of its effect. It was far more successful in suppressing inhibition from the ventro-lateral part. With this location of the stimulating electrodes inhibition was more often converted into facilitation although the initial intensity of inhibition was 1.5 times higher than during stimulation of the dorso-medial part of the head. This tendency for caffeine and amphetamine was found not only on aggregating the results of several experiments but also in a single experiment using a multiple electrode by means of which 6 or 7 points of the caudate nucleus from above downward could be tested consecutively (at intervals of 0.5-1 mm) [5].

The drugs tested, in psychostimulant doses, thus had a similar effect on the spontaneous activity of the sensomotor cortical units and produced similar changes in most indices of inhibition evoked by stimulation of the caudate nucleus, whereas they differed in their effectiveness depending on the origin of the caudate influences. It can accordingly be postulated, first, that the weakening of the inhibitory mechanisms of the caudate nucleus plays an important role in pharmacological psychostimulation and, second, that the disturbance of caudate-cortical relationships arises in different ways. Caffeine does this chiefly by direct excitation of the cortex, but amphetamine by interference with the function of the neostriatum. This is confirmed to some extent by the ability shown by caffeine in these experiments to weaken inhibition of the cortical neurons during stimulation of other cortical structures (the lateral preoptic region, the mesencephalic reticular formation), whereas amphetamine does not possess this property.

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