RELATIONSHIP BETWEEN EFFECTS OF AMPHETAMINE AND RESERPINE STUDIED ON THE CAUDATE DELAYING RESPONSE

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Chronic experiments on cats showed that the effect of amphetamine in weakening the inhibitory effects of the caudate nucleus on motor activity is preserved after administration of reserpine to the animals. Weakening of the inhibitory function of the caudate nucleus in the form of increasing the thresholds of caudate delay of movements through the action of amphetamine was more marked 24 h after injection of large doses (0.3 mg/kg) of reserpine. This could be the result of increased sensitivity of dopaminergic receptors of the nigrostriatal pathways to the mediator on the denervation principle.

KEY WORDS: basal ganglia; action of amphetamine.

Since amphetamine restores spontaneous motor activity and some forms of conditioned-reflex behavior, inhibited by reserpine, the existence of extragranular pools of mediator resistant to the action of the neuroleptic has been postulated in the presynaptic endings of noradrenergic neurons [4, 5, 10]. Similar relations between the substances evidently also take place in central dopaminergic synapses. This has been shown, in particular, by the preservation of the amphetamine stereotype, which is dopaminergic in nature, after preliminary reserpinization [7, 8].

In the investigation described below the effect of combined administration of amphetamine and reserpine on the thresholds of the delaying response to stimulation of the caudate nucleus was studied.

EXPERIMENTAL METHOD

Altogether 122 experiments were carried out on 6 unanesthetized, unrestrained cats with electrodes implanted into the head of the caudate nucleus in accordance with the coordinates of Jasper and Ajmone-Marsan's atlas [6]. Monopolar stimulation was applied to the brain as square pulses (frequency 2-10 Hz, stimulus duration 1 msec, voltage 5-25 V, for a period of 10 sec). The delaying response, in the form of arrest of spontaneous or goal-directed locomotion was recorded in response to stimulation of the caudate nucleus and assessed by a 4-point scale [1]. The localization of the electrodes was determined in serial brain sections. The pharmacological agents were injected intraperitoneally. The effect of combined administration of amphetamine and reserpine was compared with the results of control experiments in which amphetamine only was given. Altogether two series of experiments were carried out. In series I the effect of amphetamine was studied in gradually increasing doses (1, 2, and 5 mg/kg, interval between injections 20 min) 1 h after preliminary injection of a small dose (0.1 mg/kg) of reserpine (sympathomimetic phase of action of the neuroleptic), and in series II the action of the same doses of amphetamine was assessed 24 h after administration of the larger dose (0.3 mg/kg) of the neuroleptic when, in the modern view, the stable reserves of the mediator are exhausted.

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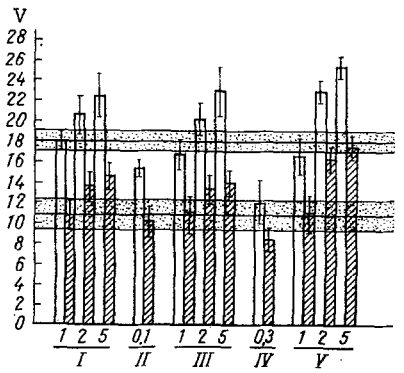

Fig. 1. Effect of combined administration of amphetamine and reserpine on thresholds of the delaying response to stimulation of the head of the caudate nucleus. Unshaded columns – mean values of thresholds (in V) with confidence limits during stimulation of caudate nucleus at a frequency of 2 pulses/sec; shaded columns show the same, with stimulation at a frequency of 10 pulses/sec; horizontal bands with dots show scatter of original values of thresholds: top band for frequency 2 pulses/sec; bottom band for frequency 10 pulses/sec; numbers beneath columns show doses of drugs (in mg/kg); I) amphetamine; II) reserpine 0.1 mg/kg; III) effect of amphetamine 1 h after injection of 0.1 μg/g reserpine; IV) reserpine 0.3 mg/kg; V) effect of amphetamine 24 h after injection of 0.3 mg/kg reserpine.

EXPERIMENTAL RESULTS

In agreement with observations by other workers [2] amphetamine, starting with a dose of 2 mg/kg, increased the thresholds of the caudate delaying response and induced a definite stereotype of behavior: turning the head from side to side, stepping from limb to limb, sniffing. With an increase in the dose, the increase in thresholds was progressive; it was more marked in the case of a lower frequency of stimulation (2 Hz; Fig. 1, I), for the intensity and frequency of the stereotyped movements were increased under these circumstances and spontaneous locomotion was virtually absent.

As the results of the combined administration of the drugs show, preliminary reserpinization did not abolish the effect of amphetamine. After injection of 0.1 mg/kg reserpine, behavioral depression developed and the thresholds of caudate delay of movements were lowered (Fig. 1, II). The action of the drug persisted for 24 h. Against this background, a small dose of amphetamine (1 mg/kg) now led to some increase in the thresholds of the delaying response. Although with an increase in the dose of the psychostimulant (2 and 5 mg/kg) the change differed only slightly from the control values, the increase in the values of the thresholds (in volts) was greater than when amphetamine alone was given (Fig. 1, III). By contrast with the control, features of stereotyped behavior, in the form of infrequent repeated movements, appeared after administration of doses starting from 1 mg/kg.

In another series of experiments, after injection of 0.3 mg/kg reserpine, the inhibitory action of the neuroleptic on behavior rose conspicuously. The thresholds of caudate delay of movements were lowered much more for both frequencies (2 and 10 pulses/sec; Fig. 1, IV); the effects lasted 10-12 days. Under these conditions, the intensity of the effect of amphetamine on behavioral delay of movements was largely dependent on its dose. After injection of the drug in a dose of 1 mg/kg, the thresholds rose significantly, although on the whole they were below the control values. More substantial changes were discovered when the dose of the drug was increased to 2 and 5 mg/kg: The values of the thresholds, when sharply reduced by reserpine, were almost doubled and were higher than both the control values and the changes produced by small doses of reserpine (Fig. 1, V). The amphetamine stereotype produced by the drug in a dose of 1 mg/kg also was much more clearly defined and more stable in character than after administration of small doses of reserpine.

Preliminary reserpinization in these experiments thus did not abolish the weakening of the delaying function of the caudate nucleus produced by amphetamine. If the dopaminergic nature of the delaying response is accepted [3], this fact can be interpreted as evidence of integrity of the processes of dopamine release from the extragranular reserves or small granular pools of the nigro-striatal pathways, which are resistant to the action of reserpine. Consequently, this phenomenon bears a close resemblance to that described in the terminals of noradrenergic neurons [4, 5, 10]. The sharp increase in the amphetamine effect 24 h after injection of 0.3 mg/kg reserpine is in agreement with observations by other workers [12-14]. This phenomenon is possibly due to an increase in the sensitivity of postsynaptic receptors to mediator and can be explained on the basis of the postulated hypersensitivity of receptors of deafferented neurons [11].

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