EFFECT OF α-METHYLTYROSINE AND DISULFIRAM ON INHIBITORY FUNCTION OF THE CAUDATE NUCLEUS AND THE CATECHOLAMINE CONCENTRATION IN THE CAT BRAIN

É. B. Arushanyan, G. V. Stolyarov, and B. A. Tolpyshev

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In unrestrained cats α-methyltyrosine (150 mg/kg) lowered the threshold of the behavioral retardation response evoked by low-frequency stimulation of the head of the caudate nucleus. This coincided with a decrease in the catecholamine level in the neostriatum and brain stem. Since a selective lowering of the brain-stem noradrenalin concentration under the influence of disulfiram (400 mg/kg) was not accompanied by any increase in the retardation of movement, it is postulated that this phenomenon depends on the state of nigro-striatal dopaminergic mechanisms. Meanwhile, both drugs facilitated the appearance of spindles on the electrocorticogram in response to stimulation of the caudate nucleus.

According to an earlier hypothesis [3], delay of movements in response to low-frequency electrical stimulation of the caudate nucleus in unanesthetized animals can be regarded as an experimental model of parkinsonism. Akinesia and rigidity, accompanying this disease, are now attributed to increased inhibitory function of the neostriatum as the result of a disturbance of nigro-striatal dopaminergic transmission [1, 7, 15].

It is therefore interesting to study the effect of inhibitors of catecholamine synthesis on the delay response and the accompanying electroencephalographic changes and also to examine the regional dopamine concentration in the brain.

EXPERIMENTAL METHOD

Two groups of experiments were carried out on unanesthetized cats. In chronic experiments on seven unrestrained animals of group 1 delay of movements was induced in response to low-frequency (2-10/sec) stimulation of the head of the caudate nucleus (for further details on the method of obtaining and assessing the response, see [2]). Meanwhile the electrical activity was recorded in the usual way in the sensomotor cortex, the contralateral caudate nucleus, and the mesencephalic reticular formation. The drugs were injected intraperitoneally 6 h before the experiment began: α-methyltyrosine (Hoffman–La Roche, Basel, Switzerland) in a dose of 150 mg/kg and disulfiram (the commercial preparation Antabuse) in a dose of 400 mg/kg. The concentrations of noradrenalin and dopamine in the caudate nucleus and brain stem were determined fluorimetrically by the method of Laverty and Sharman in the brain of 13 cats of group 2, which received similar doses of the drugs and were examined at the same times after the injection. The brain of five intact animals was used as the control.

EXPERIMENTAL RESULTS

From 2-3 h after the injection of α-methyltyrosine the animals became lethargic and their movements were limited. These phenomena reached a maximum after 5-6 h and persisted for 2 days; they closely re-

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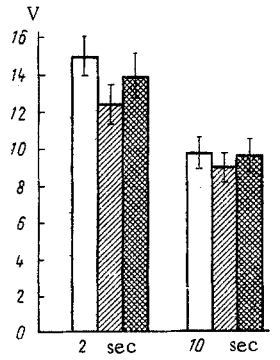

Fig. 1. Effect of α-methyltyrosine and disulfiram on threshold of the depression response to stimulation of the heat of the caudate nucleus. Columns represent mean levels of threshold (in V) with confidence limits during stimulation of the brain at 2 and 10/sec. Unshaded column – normal; obliquely shaded column – effect of α-methyltyrosine; cross-hatched column – action of disulfiram.

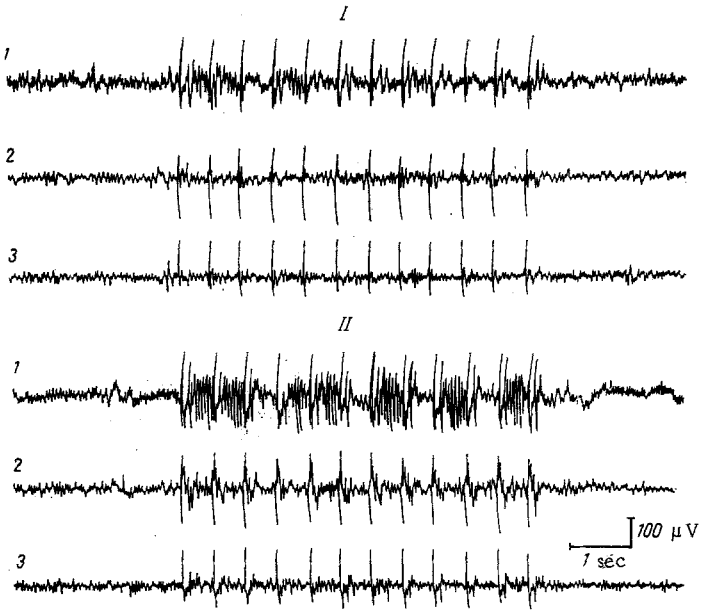

Fig. 2. Potentiation of caudate spindles by α-methyltyrosine. EEG recorded from sensomotor cortex (1), contralateral caudate nucleus (2), and mesencephalon (3); I) normal; II) 6 h after injection of drug (150 mg/kg). Horizontal line below marks stimulation of caudate nucleus (at 2/sec).

resembled the behavioral depression described by other workers [6, 12, 14]. The behavioral response and EEG changes were accordingly assessed 6 h after administration of the drug.

α-Methyltyrosine potentiated the caudate depression response as was manifested by the easier suppression of spontaneous and goal-directed locomotion. The clearest result was recorded in response to stimulation of the head of the caudate nucleus at 2/sec. The mean decrease in the response threshold was almost 3 V (Fig. 1). In response to stimulation at 10/sec the changes were less clear. In two animals multiple electrodes enabling different parts of the head of the nucleus to be stimulated consecutively in the dorso-ventral direction were used [2]. Under these conditions injection of the drug potentiated inhibition

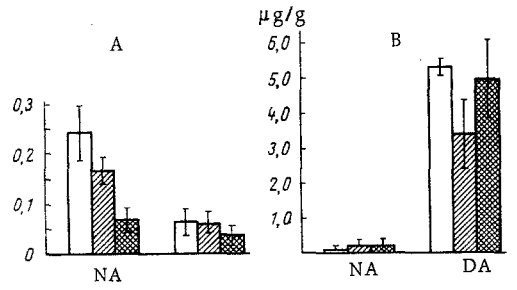

Fig. 3. Effect of α-methyltyrosine and disulfiram on regional catecholamine concentration in the brain stem (A) and caudate nucleus (B). Columns represent mean concentrations of noradrenalin (NA) and dopamine (DA) in μg/g tissue with confidence limits. Legend otherwise as in Fig. 1.

of movements developing in response to stimulation of the ventral zones by a greater degree than to stimulation of the dorsal zones.

Low-frequency stimulation of the caudate nucleus by a current sufficiently strong to produce a depression response was accompanied as a rule by the appearance of caudate spindles on the EEG of the sensomotor cortex [4]. Some workers regard this type of synchronized rhythm as an electroencephalographic index of the inhibitory function of the neostriatum [4, 8, 9].

Under the influence of α-methyltyrosine some depression of EEG activity took place, with the appearance of occasional spontaneous bursts of spindles. Meanwhile the formation of caudate spindles was considerably facilitated, in good agreement with Shellenberger's observations [13]. The effect of infrequent stimulation of below threshold strength for movement depression, unaccompanied by any marked spindle formation of the EEG, is illustrated in Fig. 2. α-Methyltyrosine led to the appearance of a series of high-amplitude potentials in response to nearly every stimulus. In some cases they appeared not only in the cortex, but also in the mesencephalic reticular formation and the contralateral caudate nucleus.

α-Methyltyrosine, which disturbs noradrenalin and dopamine synthesis in the brain [6, 12, 14], thus potentiates the behavioral and electrographic indices of the inhibitory function of the caudate nucleus. Such changes could be the result of depression of nigro-striatal dopaminergic transmission, leading to liberation of the striatal inhibitory mechanisms from the restraining control of the substantia nigra. However, another possibility cannot be ruled out. Potentiation of the inhibitory role of the caudate nucleus may also develop through primary inhibition of coupled facilitatory effects reaching the cortex through adrenergic components of the brain-stem reticular formation.

To verify this possibility a series of experiments was carried out with disulfiram. This drug blocks the conversion of dopamine into noradrenalin [5, 11] and so disturbs adrenergic transmission with significantly affecting dopaminergic transmission.

After the injection of disulfiram behavioral depression also was observed and although it appeared later, by the sixth hour it was clearly marked. In two of the five cats studied the threshold of the depression response was lowered slightly (by 1-2 V) without any appreciable change in the other responses. As a result the overall analysis revealed no changes in threshold whatever the frequency of stimulation (Fig. 1). Meanwhile the intensity of the depression, assessed in points [2], was slightly increased.

Disulfiram led to synchronization of the EEG and to the formation of spontaneous spindles. Although the drug caused no significant change in behavioral inhibition, it lowered the threshold of onset of the caudate spindles just as effectively as α-methyltyrosine. Consequently, selective blocking of adrenergic transmission by disulfiram was not noticably reflected in the depressant function of the caudate nucleus.

To estimate the character of the neurochemical changes accompanying these facts, the effect of the same doses of the drugs on the distribution of catecholamine in the brain was studied in the experiments of group 2.

The results showed, in agreement with data in the literature, that the ratio between the initial levels of dopamine and noradrenalin differs in different brain structures (Fig. 3). Under the influence of α-methyltyrosine there was a clear decrease in the dopamine concentration in the caudate nucleus and in the noradrenalin concentration in the mesencephalon. Disulfiram, on the other hand, significantly altered only the brain-stem noradrenalin concentration.

Potentiation of the caudate depression response by α-methyltyrosine thus coincided with lowering of the dopamine level in the striatum. The selective disturbance of noradrenalin synthesis by disulfiram is not reflected in this phenomenon. This suggests the role of dopaminergic mechanisms in the production of the depression, a feature which clearly brings it closer in line with parkinsonism.

On the other hand, both drugs caused a similar decrease in the thresholds of appearance of caudate spindles in the cortex. α-Methyltyrosine can evidently do this directly, by inhibiting nigro-striatal dopam-

inergic transmission, whereas disulfiram does so by depressing coupled reticulo-cortical activating impulses. This dissociation in their action on the behavioral and electrographic indices of the inhibitory function of the caudate nucleus is another argument in support of the probability that the depression response can occur without the need for involvement of the neocortex.

LITERATURE CITED

1. É. B. Arushanyan, Zh. Nevropat. i Psikhiat., 72, 601 (1972).
2. É. B. Arushanyan, Yu. A. Belozertsev, and B. A. Tolpyshev, Zh. Vyssh. Nerv. Dayat., 22, 374 (1972).
3. É. B. Arushanyan, G. V. Stolyarov, and B. A. Tolpyshev, Zh. Nevropat. i Psikhiat., 70, 1384 (1970).
4. N. A. Buchwald, E. J. Wyers, C. W. Lauprecht, et al., Electroenceph. Clin. Neurophysiol., 13, 531 (1961).
5. M. Goldstein, B. Anagnoste, E. Lauber, et al., Life Sci., 3, 763 (1964).
6. L. C. F. Hanson, Psychopharmacologia (Berlin), 8, 100 (1965).
7. O. Hornykiewicz, Pharmacol. Rev., 18, 925 (1966).
8. F. G. Horvath, S. Soltysik, and N. Buchwald, Electroenceph. Clin. Neurophysiol., 17, 670 (1964).
9. A. Kitsikis, F. G. Horvath, and A. Rougeul, Electroenceph. Clin. Neurophysiol., 25, 160 (1968).
10. R. Laverty and D. F. Sharman, Brit. J. Pharmacol., 24, 759 (1965).
11. J. Musacchio, I. J. Kopin, and S. Snyder, Life Sci., 3, 769 (1964).
12. R. H. Rech, H. K. Borys, and K. E. Moore, J. Pharmacol. Exp. Ther., 153, 412 (1966).
13. M. K. Shellenberger, Neuropharmacology, 10, 347 (1971).
14. S. Spector, A. Sjoerdsma, and S. Udenfriend, J. Pharmacol. Exp. Ther., 147, 286 (1965).
15. G. Steg, Acta Neurol. Scand., 48, Suppl. 51, 139 (1972).