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For a generous supply of α-methyldopa we thank Merck, Sharp and Dohme.

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March 23, 1967

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Reversal of α-methyltyrosine-induced behavioural depression with dihydroxyphenylalanine and amphetamine

SIR,—The time course and the degree of behavioural depression following administration of α-methyltyrosine correlates with the reduced brain levels of noradrenaline and dopamine (Hanson, 1965; Moore, 1966). Nevertheless, many factors must be considered before this behavioural deficit can be causally related to a lack of brain catecholamines. For example, toxicity (Weissman & Koe, 1965) and direct depressant actions of α-methyltyrosine could contribute to the behavioural effects. However, with proper precautions it can be shown that these factors do not play a major role in the behavioural effects of this drug. Multiple injections of small doses of α-methyltyrosine produced behavioural depression and catecholamine depletion without concomitant toxicity (Rech, Borys & Moore, 1966). The importance of a direct depressant action of α-methyltyrosine was minimized by the finding that pretreatment with monoamine oxidase inhibitors reduced both the catecholamine-depleting and behavioural depressant effects of this drug without altering the concentration of α-methyltyrosine in the brain (Moore & Rech, 1967). Further efforts to implicate brain catecholamines in the central actions of α-methyltyrosine are described in this communication. It will be shown that both dihydroxyphenylalanine (L-dopa), which serves as an immediate precursor for dopamine and noradrenaline, and (+)-amphetamine, which mimics the actions of catecholamines, at least at peripheral sites, reverse α-methyltyrosine-induced behavioural depression.

Female rats (CD_1, Charles River Animal Farm), 175–200 g, were trained to perform in a shuttle box. Each trial was initiated by activating a small light on the side of the cage occupied by the animal. After 5 sec of light the grid floor on the same side of the cage was electrified for 5 additional sec. If the rat moved to the unlighted side during the initial 5 sec, the response was termed

an "avoidance"; if the animal shuttled during the latter 5 sec of the trial the response was termed an "escape." The trials were repeated every 30 sec; 20 such trials constituted a test session. After 10 training sessions 25 rats, which averaged better than 16 avoidance responses per session, were selected for the experiment. After the test session at zero time each rat received 3 intraperitoneal injections of an aqueous suspension of α-methyltyrosine (50 mg/kg) at 4 hr intervals (at 0, 4 and 8 hr) indicated by the black arrows in Fig. 1. This dosage schedule was previously shown to cause a progressive reduction of brain stores of noradrenaline and dopamine and to impair conditioned avoidance behavioural responses; the maximum effect was seen at 12 hr (4 hr after the last injection) and recovery was complete by 24 hr (Rech & others, 1966). Fifteen animals were tested in the shuttle box at 12 hr and then injected with saline (5 rats), 100 mg/kg L-dopa (8 rats) or with 0·5 mg/kg of (+)-amphetamine sulphate (7 rats). All drugs were injected intraperitoneally. One-half hr later these rats were retested in the shuttle box. As seen in Fig. 1, 3 injections of α-methyltyrosine much reduced the number of avoidances per session and caused a loss of 1–4 escape responses. There was no change in this behaviour pattern after saline (Fig. 1a) but both L-dopa and (+)-amphetamine (Fig. 1b, c) restored escape responses and caused a significantly greater number of avoidance responses. That is, in these animals the number of avoidances per session were significantly higher ($P < 0.05$) at 12½ hr than at 12 hr (Student's t test). In another 5 rats, α-methyltyrosine was administered in the same manner but the animals were tested in the shuttle box at 11½ hr after the first dose (Fig. 1d). The extent of depression was about the same as in the previous tests. Immediately after this test each animal was injected with 100 mg/kg L-dopa and tested 1 hr later. At this time (12½ hr after the first α-methyltyrosine injection) the depression from α-methyltyrosine was completely antagonized.

α-Methyltyrosine blocks catecholamine biosynthesis at the tyrosine hydroxylase step; the subsequent enzymatic steps are unaffected (Udenfriend, Zaltman-

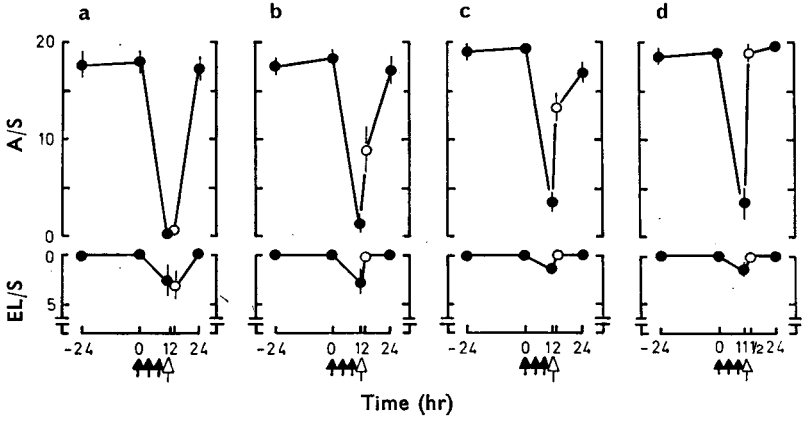

FIG. 1. Effects of L-dopa and (+)-amphetamine on depressed conditioned avoidance behaviour in rats treated with α-methyltyrosine. α-Methyltyrosine (50 mg/kg) was injected at 0, 4 and 8 hr (black arrows). In a, b and c, rats were injected with saline, L-dopa (100 mg/kg) or (+)-amphetamine (0·5 mg/kg) respectively at 12 hr (open arrows) and tested 30 min later. In d, rats were injected with L-dopa at 11·5 hr, and retested 1 hr later. The points represent mean values for each group and the vertical lines the standard errors. Where no line is shown the standard error is less than the radius of the point. A/S avoidance per session; EL/S escapes lost per session.

Nirenberg & others, 1966). Thus L-dopa should enter the biosynthetic pathway below the block and through the processes of decarboxylation and hydroxylation form dopamine and noradrenaline. Using the same dose as reported here, Corrodi, Fuxe & Hökfelt (1966) showed that L-dopa restored the noradrenaline and dopamine content of brains that had been depleted by α-methyltyrosine. The reversal of the behavioural depression by L-dopa may well be secondary to the restoration of these catecholamines in the brain.

Although α-methyltyrosine has been reported to possess potent anti-amphetamine actions (Weissman, Koe & Tenen, 1966) it is obvious that under the conditions of the present experiments amphetamine adequately reversed the depression it induced. Poschel & Ninteman (1966) reported that methylamphetamine reversed the suppression of self-stimulation it caused. The mechanism of the amphetamine reversal is poorly understood. Perhaps (+)-amphetamine mimics the effects of noradrenaline or dopamine at central receptor sites or is able to release residual stores of catecholamines from nerve terminals in the brain. In any case, it is of interest that certain behavioural responses that are depressed by α-methyltyrosine are restored by (+)-amphetamine, while in other behavioural situations a stimulant effect of (+)-amphetamine is antagonized by pretreating with α-methyltyrosine.

These results, along with the reports cited above, strengthen the proposal that α-methyltyrosine-induced behavioural depression occurs as a consequence of the lack of noradrenaline or dopamine, or both, in the brain.

Acknowledgements. This work was supported by Grants AM 11083 and NB 06013 from USPHS.

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February 23, 1967

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