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Short Communication

Inhibition of Brain Protein Synthesis by Doses of L-DOPA that Disaggregate Brain Polyribosomes

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Summary

Rats receiving doses of L-DOPA sufficient to cause disaggregation of brain polyribosome profiles exhibit *in vivo* inhibition of uptake of ^{14}C-leucine or ^{14}C-lysine into brain protein coincident with the disaggregation.

We have shown that, following administration of L-DOPA to rats, polyribosomes prepared from brain show disaggregation (*Weiss et al.*, 1971). The disaggregation phenomenon occurs maximally at 20—60 minutes after L-DOPA administration and thus coincides with the period over which excess L-DOPA can be detected by standard procedures in the brain. The disaggregation occurs in infant rats of 7—19 days of age (weight 15—20 gm) following 50 mg DOPA/kg body weight; whereas at 19—22 days of age (45—55 gm body weight), administration of 200 mg DOPA/kg body weight fails to cause disaggregation, and older animals weighing 100—120 gm required 500 mg/kg to produce disaggregation. Since rats show metabolic parameters some five-fold that of man, the latter dose is comparable to the dose-levels administered to human cases of Parkinson's disease, namely 6—8 gm/day. By use of inhibitors we have shown that the mechanism of disaggregation involves conversion to dopamine.

Hartmann and Becker (1973) have recently published electron microscopic data on polysome aggregation in the brain which purports to show that the disaggregation caused by L-DOPA and by L-phenylalaline (*e.g. Aoki* and *Siegel*, 1970) is artifactual and cannot be seen on E.M. pictures of intact brain cells following such treatments. They

administered 100 mg/kg L-DOPA to rats of an unspecified strain and sex weighing 30—40 gm and said to be 7—10 days old, and observed no loss of ribosome aggregates on E.M. pictures of the brain.

In order to decide between this conflicting evidence regarding polysome disaggregation in vivo after L-DOPA administration, an independent demonstration of inhibition of incorporation of amino acids into brain proteins would be compelling. This would complement the evidence of change in polysome structure by showing that that any alterations were reflected in the physiological function of these organelles to make protein.

Rats weighing 40 gm were injected with 500 mg/kg L-DOPA in 0.05 N HCl or 0.05 N HCl intraperitoneally and 45 minutes later received 1.5 μCi ^{14}C-leucine (U) or 1.5 μCi ^{14}C-lysine (U) intracisternally in 20 μl 0.05 M Tris buffer (pH 7.4), killed 30 minutes later, that is 75 minutes after L-DOPA administration. The brains were removed, a portion was assayed for TCA-precipitable protein and another portion was taken for polysome isolation. The proportion of brain ribosomes found as polyribosomes was 64 % for animals injected with 0.05 N HCl, but fell to 28 % in L-DOPA treated animals. Uptake of ^{14}C-lysine into TCA-precipitable protein was reduced to 37 % of uptake by the control brains and in the case of ^{14}C-leucine to 78 % of control values. Both these differences were significant ($p < 0.001$ and $p < 0.05$, respectivelty). These differences were not due to changes in precursor amino acid specific activity. Studies on animals killed at various times from 52 minutes through 270 minutes after L-DOPA administration showed that the depression of uptake of ^{14}C-lysine persisted for as long as 2 hours, coincident with the duration of DOPA-induced polysome disaggregation, but at 150 minutes had returned to normal, and at this time polysome disaggregation was no longer observed.

The failure of Hartmann and Becker to observe disaggregation by electron microscopy may be due to inadequate dosage of DOPA to animals weighing 30—40 gm, since they gave 100 mg/kg, and we noted (*Weiss et al.*, 1971) that animals of 45—55 gm required more than 200 mg/kg to produce disaggregation. In addition, the E.M. procedure is not quantitative; since L-DOPA causes about 50 % reduction in aggregated polyribosomes and not total disaggregation, the phenomenon may be below the limit of sensitivity of the E.M. technique to detect such alteration.

References

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