Biochemical evidence for the involvement of noradrenaline in motor activity produced by L-DOPA in rodents

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The beneficial effects of L-DOPA therapy in Parkinsonian patients have been attributed to the replacement of cerebral dopamine (DA). However, considerable experimental evidence suggests that both noradrenergic and dopaminergic neurotransmission are involved in the control of gross motor activity. We have previously presented behavioural and biochemical evidence to suggest the involvement of a noradrenergic component in the L-DOPA reversal of reserpine-induced akinesia in mice (Dolphin, Jenner & Marsden, 1975). We now extend these studies to include biochemical evidence which suggests that L-DOPA induces functional changes in noradrenaline (NA) turnover. Normal mice ('Swiss s' or 'p' strain male), or those pre-treated with reserpine (10 mg/kg, i.p.) 19 h previously, or α-methylparatyrosine (AMPT) (200 mg/kg, i.p.) 3 h previously, were given L-DOPA (200 mg/kg in methylcellulose i.p.) plus MK486 (α-methyldopahydrazine (25 mg/kg, i.p.)). In all cases a significant increase in whole brain DA was observed 1 h after L-DOPA.

Cerebral NA levels were also significantly increased in reserpinized mice, from 19 ± 6 ng/g to 46 ± 13 ng/g ($P < 0.05$); and in AMPT-treated mice from 249 ± 84 ng/g to 501 ± 108 ng/g ($P < 0.025$).

This increase was prevented by the dopamine-β-hydroxylase inhibitor FLA-63 (bis-(1-methyl 4 homopiperazinyl thiocarbonyl) disulphide) administered 1 h before L-DOPA.

In contrast the same dose of L-DOPA produced no change in NA in normal animals (from 611 ± 43 ng/g to 630 ± 63 ng/g), although pre-treatment with pargyline (200 mg/kg, i.p.) resulted in a significantly greater rise in NA 1 h after L-DOPA (1148 ± 175 ng/g) compared with animals given pargyline alone (832 ± 29 ng/g $P < 0.05$).

Whole brain 4-methoxy 3-hydroxyphenylglycol sulphate (MOPEG-SO_4) measured 2 h after administration of L-DOPA (200 mg/kg) + MK486 (25 mg/kg) was unaltered in normal and AMPT-treated male Wistar rats, but was significantly decreased in reserpinized rats (22 ± 3 ng/g) compared to controls (53 ± 4 ng/g; $P < 0.0125$). However, in agreement with Keller, Bartholini & Pletscher (1974), elevation in whole brain MOPEG-SO_4 was found 2 h after a lower dose of L-DOPA (50 mg/kg, i.p.). This was significant in reserpinized rats (90 ± 12 ng/g) compared to controls (53 ± 4 ng/g; $P < 0.025$) and in AMPT-treated rats (125 ± 6 ng/g) compared to controls (75 ± 7 ng/g; $P < 0.0005$). The increase in brain MOPEG-SO_4 after a small dose of L-DOPA was prevented by prior administration of FLA-63.

Measurement of forebrain homovanillic acid (HVA): 3,4-dihydroxyphenylacetic acid (DOPAC) ratios in mice suggested that 2 h after the high dose of L-DOPA the enzyme catechol-*O*-methyl transferase (COMT) was markedly inhibited; the HVA/DOPAC ratio (0.19 ± 0.02) was significantly lower than that found in normal animals (1.01 ± 0.19), or 2 h after the lower dose of L-DOPA (0.87 ± 0.27).

These findings confirm that increased NA turnover does occur after L-DOPA in normal and amine-depleted animals. It cannot be detected by measuring MOPEG-SO_4 levels, after high doses of L-DOPA because these inhibit COMT, thereby preventing the formation of this metabolite of NA.

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References

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