Inhibition of the anticonvulsant activity of L-dopa by FLA-63, a dopamine-β-hydroxylase inhibitor

Recently it has been shown that whereas L-dopa and (+)-amphetamine protect mice against maximal electroshock treatment (MES), apomorphine does not (McKenzie & Soroko, 1972). Assuming that apomorphine is a selective dopamine-like agonist, a concept supported by a number of authors (Ernst, 1965, 1969; Ernst & Smelik, 1966; Andén, Rubenson & others, 1967; Ungerstedt, Butcher & others, 1969; Roos, 1969), it was concluded that the anticonvulsant activity of L-dopa may be unrelated to its pharmacological activity on dopaminergic neurons.

A possible mechanism for the anticonvulsant effects of L-dopa could be an increased synthesis of noradrenaline in central noradrenergic neurons. Such a mechanism could be interrupted by inhibiting dopamine -β-hydroxylase, the enzyme catalysing the hydroxylation of dopamine to form noradrenaline. To test this hypothesis, we studied the effects of FLA-63, bis(4-methyl-1-homopiperazinylthiocarbonyl)disulphide, a dopamine-β-hydroxylase inhibitor, on the anticonvulsant activity of pargyline plus L-dopa.

Carworth Farms (CF1), white, male mice, 20–22 g, were used. MES was given using a Hans Seizure Apparatus and corneal electrodes through which was applied 50 mA for 0·2 s. Animals were pretreated using the following schedule. Pargyline, in saline, i.p., 3 h before MES; FLA-63, in saline i.p., 2 h before MES; L-dopa, in 0·1 N HCl, s.c., 1 h before MES. Control animals received appropriate volumes of all diluents at the prescribed pretreatment times. Animals were considered protected if the hindlimb extensor component was blocked. The latency of the hindlimb extension i.e. the interval between shock application and hindlimb extension, was recorded in those animals not protected.

The results are shown in Table 1. Control animals responded to MES with 0% protection and a mean latency to tonic extension of 1·97 ± 0·10 s (mean ± s.e.). Pargyline-pretreated animals did not differ significantly from controls. The combined treatment with pargyline, 50 mg kg^{-1}, and L-dopa, at 80 or 100 mg kg^{-1}, pro-

Table 1. *Effects of FLA-63 pretreatment on the anticonvulsant activity of pargyline + L-dopa.*

Group	Drug (Dose mg kg^{-1})	% Protected (n)	Latency (n)	Comparison	*P*
A	Diluents	0 (10)	1·97 ± 0·10 (10)	—	—
B	Pargyline (50)	0 (30)	1·93 ± 0·06 (30)	B–A	N.S.
C	Pargyline (50) + FLA-63 (50)	0 (38)	0·92 ± 0·02 (38)	C–B	<0·001
D	Pargyline (50) + L-dopa (80)	57 (30)	2·77 ± 0·13 (13)	D–B	<0·01
E	Pargyline (50) + L-dopa (100)	95 (39)	2·80 ± 0·40 (2)	—	—
F	Pargyline (50) + FLA-63 (50) + L-dopa (80)	0 (40)	1·69 ± 0·07 (40)	F–B	<0·02
G	Pargyline (50) + FLA-63 (50) + L-dopa (100)	26 (34)	2·17 ± 0·17 (25)	G–B	N.S.

Latencies are expressed in seconds - mean ± s.e. *P* values were calculated using Student's *t*-test.

tected 57 and 95% of the animals, respectively. The 13 animals of group D (Table 1) which were not protected by L-dopa, had an increased mean latency of 2·77 ± 0·13, which was significantly longer than pargyline-treated animals.

In contrast, the combined treatment with pargyline and FLA-63, 50 mg kg^{-1} each (Group C), produced a marked decrease in the mean latency to 0·92 ± 0·02 s. This difference was highly significant when compared to either the pargyline group or the control group. In addition, pretreatment with FLA-63 completely blocked the anticonvulsant effects of L-dopa at the 80 mg kg^{-1} dose and reduced the per cent protected following the 100 mg kg^{-1} dose from 95 to 26%. The mean latency of animals receiving pargyline, FLA-63 and L-dopa (100 mg kg^{-1}) did not differ significantly from pargyline-treated animals.

Pretreatment with FLA-63 decreased markedly the latency to hindlimb tonic extension. This proconvulsant effect of a dopamine-β-hydroxylase inhibitor has been demonstrated previously by Rudzik & Johnson (1970) using U-14 624 (1-phenyl-3-(2-thiazolyl)-2-thiourea), a dopamine-β-hydroxylase inhibitor structurally different from FLA-63. These findings suggest that low noradrenaline concentrations increase the susceptibility of animals to electroshock-induced seizures.

The anticonvulsant effect of pargyline plus L-dopa was either completely blocked or reduced markedly in animals pretreated with FLA-63. Other authors have shown that, in nialamide-treated rats, FLA-63 in the dose range used by us, reduces noradrenaline levels in the cns by approximately 75% whereas, dopamine levels were not different from nialamide-treated animals (Andén & Fuxe, 1971). Furthermore, the administration of L-dopa did not replenish the noradrenaline stores despite large increases in dopamine levels (Andén & Fuxe, 1971). These results can be interpreted to mean that an intact noradrenaline synthesis is required for the anticonvulsant activity of L-dopa.

It is hazardous to draw definitive conclusions from studies involving multiple drug treatments. However, our results strongly suggest that the anticonvulsant activity of L-dopa, in mice, is mediated by its pharmacological effects on noradrenergic neurons rather than dopaminergic neurons. This conclusion is in agreement with the concept of Rudzik & Johnson (1970) that convulsive thresholds to electroshock depend upon brain concentrations of noradrenaline and suggests a tentative explanation for the lack of anticonvulsant activity of apomorphine in the mouse.

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