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The antidyskinetic action of dihomo-γ-linolenic acid in the rodent

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1 The antidyskinetic action of dihomo-γ-linolenic acid (DHLA) was assessed against dyskinesias induced in the guinea-pig by dopamine injected into the striatum (200 μg bilateral 2 h after nialamide, 75 mg kg^{-1}, i.p.) and in the guinea-pig and rat by 2-di-*n*-propylamino-5, 6-dihydroxytetralin (tetralin), 0.025 mg kg^{-1}, s.c.

2 Dopamine and tetralin-induced dyskinesias in the guinea-pig were reduced or abolished by DHLA given i.p., 30–100 mg kg^{-1}, given once daily for 5–10 days.

3 Tetralin-induced dyskinesias were antagonized by DHLA given orally to the guinea-pig (50–200 mg kg^{-1}, 5 days) or in the diet to the rat (approximately 200 mg kg^{-1} daily for 10–14 days).

4 DHLA injected into the striatum (2.5–20 μg bilateral, 2–4 days) also antagonized tetralin-induced dyskinesias in the rat.

5 The antidyskinetic action of DHLA given i.p. to the guinea-pig could be antagonized by aspirin or eicosa-5,8,11,14-tetraynoic acid (100 mg kg^{-1} i.p. daily, starting 2 days before a 5 day treatment with DHLA). Aspirin (25–100 mg kg^{-1}, i.p.) dose-dependently antagonized the antidyskinetic activity of 5 and 20 μg DHLA given bilaterally into the striatum (2 days).

6 DHLA (100 mg kg^{-1} i.p.) given daily for 10 days or approximately 200 mg kg^{-1} DHLA (daily for 10–14 days given in the diet) administration to the rat failed to modify the stereotyped behaviour induced by apomorphine, 0.5 or 2 mg kg^{-1} s.c., to induce catalepsy, or to modify the cataleptic effects of haloperidol 0.25 or 1 mg kg^{-1} i.p.

7 It is suggested that the selective inhibition of dyskinesias in the rodent by DHLA may reflect a striatal effect with a dependency on conversion to prostaglandins.

Introduction

Tardive dyskinesias, often characterized by involuntary oro-bucco-lingual movements, occur in schizophrenic and other patients following long-term neuroleptic treatment. The subject has been exhaustively reviewed and most authors have concluded a causal relationship between the administration of the neuroleptic agents and the subsequent late development of abnormal involuntary movement disorders (Baldessarini *et al.*, 1979; Gerlach, 1979; Jeste & Wyatt, 1982; Kane & Smith, 1982). The generally persistent nature of the dyskinesias and the absence of a satisfactory treatment has caused considerable concern. The most effective treatment remains to increase the dose of neuroleptic agent, the causative agent, with the immediate potential difficulties of inducing other extrapyramidal side effects, e.g. akinesia, and posing even further questions as to the exacerbation of dyskinesias in the long-term (Baldessarini *et al.*, 1982; Simpson *et al.*, 1982).

The tardive dyskinesias related to neuroleptic treatment are similar in nature to those induced by L-DOPA and dopamine agonists (Goetz, 1983; Karson *et al.*, 1983) and, whilst accepting that the dyskinesias may involve different pathophysiological mechanisms (Karson *et al.*, 1983), both types of dyskinesias are thought to reflect an absolute or relative enhancement of dopamine function in those brain areas relevant to motor control, in particular, the striatum. Whilst conjectural, this hypothesis is supported by studies in laboratory animals showing that the injection of dopamine agonists into the striatum can cause dyskinesias (Costall *et al.*, 1975; 1980a).

The approach to dyskinesia antagonism is therefore to reduce the function of dopamine in the striatum. The difficulties of using postsynaptic dopamine receptor antagonists lead to a search for other naturally occurring substances/neuromodulators which may

reduce the activity of dopamine in the striatum. The work of Schwarz *et al.* (1982) showed that the prostaglandins could reduce striatal dopamine function. In the present study we have investigated the ability of dihomo-γ-linolenic acid (DHLA), a precursor of the prostaglandin 1 and 2 series, to antagonize the abnormal involuntary movements induced by dopamine agonists in the rat and guinea-pig.

Methods

Male Sprague-Dawley (C.D., Bradford Strain) rats weighing 300 ± 25 g and male Dunkin-Hartley (Bradford Strain) guinea-pigs weighing 500 ± 50 g were used.

Stereotaxic surgery

Rats (anaesthetized with chloral hydrate, 300 mg kg^{-1} i.p.) and guinea-pigs (anaesthetized with sodium pentabarbitone, 30 mg kg^{-1} i.p.) were subject to standard stereotaxic surgery for the implantation of chronically indwelling guide cannulae for subsequent bilateral injection into the caudate-putamen (rat: Ant. 7.4, Vert. 1.0, Lat. ±3.0: De Groot, 1959; guinea-pig Ant. 8.0, Vert. +6.8, Lat. ±2.5; Costall *et al.*, 1980a). Guides (implanted 2.0 mm above the injection site) were made from 0.65 mm external diameter stainless steel tubing held in perspex blocks and fixed to the skull by anchor screws and dental acrylic cement. During a 14 day postoperative recovery period guides were kept patent by 0.32 mm external diameter stainless steel stylets which extended 0.5 mm below the guide tips. For intracerebral drug injection, animals were manually restrained, stylets removed and replaced by injection units (0.32 mm stainless steel tubing) which allowed the bilateral delivery of drug or vehicle into the caudate-putamen via Agla micrometer syringes in 1–2 μl over a 1 min period; stylets were then replaced.

Measurement of dyskinesias, stereotyped behaviour and catalepsy

Dyskinesias were induced in the guinea-pig by 200 μg dopamine injected into the striatum 2 h after treatment with nialamide, 75 mg kg^{-1} i.p. (initial studies assessed the actions of 5–400 μg dopamine; 200 μg was selected as the lowest dose to cause a consistent dyskinesia score of 3 in all animals, see below) or by 2-di-*n*-propylamino-5, 6-dihyroxytetralin (tetralin), 0.025 mg kg^{-1} s.c. (effects of 0.00625–0.5 mg kg^{-1} were assessed in preliminary studies and 0.025 mg kg^{-1} selected as the lowest dose causing a dyskinesia score of 3 in all animals). The same dose of the tetralin compound was used (for the same reason) to induce dyskinesias in the rat. Both the intrastriatal dopamine and the peripheral tetralin treatments caused the development of perioral movements (termed dyskinesias) which involved gnawing/biting reactions with occasional protrusion of the tongue, with or without licking movements. These movements were not usually directed onto physical material.

To assess the intensity of dyskinesias animals were observed for a 30 s period and score of 1 was allocated to a weak response in which an animal demonstrated occasional perioral movements, score of 2 to a moderate intensity response in which the periods of perioral movements were dominant but clearly broken by brief periods when the perioral movements were absent, and score of 3 was allocated to an intense response where the perioral movements were continuous. Dopamine dyskinesias were assessed at 10 min intervals from onset (2 h) for 90 min, tetralin dyskinesias at 5 min intervals from onset (20 min) for 45 min. The mean dyskinesias score was determined for each animal and then for each group of animals.

Stereotyped behaviour was induced in the rat by apomorphine (0.25–2.0 mg kg^{-1}, s.c.) and was scored: 0 = no stereotypy; 1 = discontinuous sniffing and/or repetitive head and limb movements; 2 = continuous sniffing and/or repetitive head and limb movements; 3 = periodic biting or licking and 4 = continuous biting or licking. The biting and licking responses were generally directed at the cage sides or shavings.

Catalepsy was induced in the rat by haloperidol (0.25–2.0 mg kg^{-1}, i.p.) and measured by carefully placing the rat with its front limbs extended over a 10 cm high bar and noting the time the animal maintained the imposed position. Animals were tested every 30 min and in order to account for animals maintaining the imposed position for an 'infinite' period of time a scoring system was adopted to estimate the intensity of catalepsy: 0 = no catalepsy, 1 = 0.1–2.5 min, 2 = 2.6–5.0 min. 3 = 5.1–10.0 min, 4 = 10.1–20.0 min, 5 = 20.1 + min.

Experimental design

Rats and guinea-pigs were normally housed in groups of 3 to 5. For visual assessment of dyskinesia intensity (between 10 h 30 min and 16 h 30 min) they were placed in individual perspex cages measuring 25 × 14 × 14 cm in a diffusely illuminated, soundproofed room maintained at 21–23 °C. Preliminary experiments established that DHLA treatment for less than 5 days failed to modify the dyskinesias. Therefore in subsequent studies the antagonism of

dopamine and tetralin dyskinesias in the guinea-pig was determined after i.p. (5–10 days treatment) and oral (5 days treatment) administration of DHLA (given 4 h before dopamine or tetralin). The abilities of aspirin and eicosa-5,8,11,14-tetraynoic acid (ETYA) (given for 7 days) to modify the effects of DHLA given i.p. (given for 5 days, commencing on day 3 of aspirin or ETYA treatment) were determined. DHLA was given 20 min after the aspirin or ETYA. The antidyskinetic action of DHLA injected into the striatum (given for 1–4 days) and its antagonism by aspirin (given for 3 days, DHLA for 2 days) were also assessed in the rat. The effectiveness of DHLA in the diet (14 days) was investigated by placing the rats in individual cages having specially designed feed trays which allowed the rats to feed freely on DHLA-containing diet (palmitic acid control, see below) whilst spillage was collected. The amount of diet uneaten was determined daily.

The ability of DHLA to modify apomorphine-induced stereotypy or haloperidol-induced catalepsy was assessed after administration of DHLA (100 mg kg^{-1} i.p. for 10 days) or in the diet (approximately 200 mg kg^{-1} daily for 14 days).

The significance of differences between responses was assessed by one-way ANOVA followed by Dunnett's test for multiple comparisons, or by application of the Student's *t* test.

Drugs

Dopamine HCL (Sigma) was prepared for intrastriatal injection in a nitrogen bubbled solution containing 0.01% sodium metabisulphite, 2-di-*n*-propylamino-5, 6-dihydroxyteralin, HBr (tetralin, Glaxo) and apomorphine HCl (Sigma) were similarly prepared for s.c. injection using 0.1% sodium metabisulphite. Haloperidol (Janssen) was prepared for i.p. injection in 1% lactic acid. Nialamide was dissolved in a minimum quantity of hydrochloric acid and made up to volume with distilled water. DHLA (98% purity, Roche) was prepared for i.p., oral and intrastriatal administration as a temporary emulsion in water by homogenization using a Polytron (setting No. 5) and was used immediately. Aspirin (B.P.) was prepared in solution using a minimum quantity of sodium citrate, and ETYA (Ro 03–1428, Roche) was prepared as a suspension in 2% carboxymethyl cellulose (homogenized using a Polytron, setting 5, to reduce particle size). Intrastriatal administration was in a volume of 1–2 μl, peripheral administration in a volume of 1–2 ml kg^{-1}.

DHLA was prepared in the diet using the formulation B.P. powdered guinea-pig diet (B.P. Nutrition, Witham, Essex) 100 g, salt 0.2 g, lard 9.0 g, DHLA 1.0 g (or palmitic acid 1.0 g for control animals). Balls of diet were prepared by melting the lard and adding water. Diet was prepared every 2–3 days and stored at 0–4 °C. Uneaten diet was removed daily.

Results

Antagonism of dyskinesias by daily systemic administration of DHLA to the guinea-pig: modification by aspirin and ETYA

DHLA, 30–100 mg kg^{-1} i.p. daily, given for 5 or 10 days, dose-dependently reduced the intensity of dys-

Table 1 Antagonism of dyskinesias following daily systemic administration of dihomo-γ-linolenic acid (DHLA) to the guinea-pig

Dose of DHLA (mg kg^{-1} i.p.)	*Duration of treatment* (days)	*Dopamine dyskinesias* (mean score ± s.e.mean $n=6-12$)	*Tetralin dyskinesias* (mean score ± s.e.mean $n=6-12$)
Vehicle	5	2.9 ± 0.03	2.9 ± 0.07
10	5	2.8 ± 0.03	2.9 ± 0.03
30	5	2.5 ± 0.22	2.0 ± 0.08*
50	5	1.6 ± 0.12**	1.2 ± 0.17**
75	5	0.3 ± 0.07**	0.3 ± 0.05**
100	5	0.1 ± 0.01**	0.0 ± 0.0**
Vehicle	10	2.9 ± 0.03	2.8 ± 0.05
10	10	2.8 ± 0.08	2.8 ± 0.07
30	10	1.7 ± 0.15**	1.7 ± 0.15*
50	10	1.3 ± 0.12**	0.8 ± 0.08**
75	10	0.3 ± 0.02**	0.2 ± 0.03**
100	10	0.0 ± 0.0**	0.0 ± 0.0**

Significant reduction in dyskinesias from vehicle control values indicated as *$P<0.05$; **$P<0.01$–$P<0.001$ (one-way ANOVA followed by Dunnett's test for multiple comparisons).

Table 2 Antagonism of the antidyskinetic action of dihomo-γ-linolenic acid (DHLA) in the guinea-pig by aspirin

Dose of DHLA (mg kg^{-1} i.p.)	*Dose of aspirin* (mg kg^{-1} i.p.)	*Dopamine dyskinesias* (mean score ± s.e. mean $n=6$)	*Tetralin dyskinesias* (mean score, ± s.e. mean $n=6$)
Vehicle	Vehicle	2.8 ± 0.09	2.8 ± 0.05
Vehicle	100	2.8 ± 0.05	3.0 ± 0.0
50	Vehicle	1.2 ± 0.11	1.0 ± 0.08
50	100	2.5 ± 0.04*	2.7 ± 0.31*
75	Vehicle	0.3 ± 0.04	0.3 ± 0.11
75	100	2.7 ± 0.32*	2.8 ± 0.07*
100	Vehicle	0.2 ± 0.01	0.0 ± 0.0
100	100	2.2 ± 0.08*	2.3 ± 0.21*

The antidyskinetic actions of DHLA were significantly antagonized by the aspirin treatment (*$P<0.001$ compared with vehicle controls at each DHLA dose, Student's t test).

Table 3 Antagonism of the antidyskinetic action of dihomo-γ-linolenic acid (DHLA) in the guinea-pig by eicosa-5, 8,11,14-tetraynoic acid (ETYA)

Dose of DHLA (mg kg^{-1} i.p.)	*Dose of ETYA* (mg kg^{-1} i.p.)	*Dopamine dyskinesias* (mean score ± s.e.mean $n=6$)	*Tetralin dyskinesias* (mean score ± s.e.mean $n=6$)
Vehicle	Vehicle	2.8 ± 0.08	2.8 ± 0.09
Vehicle	100	2.8 ± 0.03	2.8 ± 0.09
50	Vehicle	1.0 ± 0.02	1.3 ± 0.17
50	100	2.8 ± 0.17*	2.7 ± 0.23*
75	Vehicle	0.3 ± 0.04	0.3 ± 0.08
75	100	3.0 ± 0.06*	2.8 ± 0.04*
100	Vehicle	0.0 ± 0.0	0.0 ± 0.0
100	100	2.5 ± 0.08*	2.3 ± 0.22*

The antidyskinetic actions of DHLA were significantly antagonized by the ETYA treatment (*$P<0.001$ compared with vehicle controls at each DHLA dose, Student's t test).

kinesias induced either by dopamine injected into the striatum or tetralin given s.c. to the guinea-pig. Indeed, the highest dose of DHLA used was able to abolish dyskinesia responding (Table 1). This antagonism of dyskinesias was not apparent when DHLA was administered daily for 4 days or less, and clear antagonism recorded after 5 days was only slightly increased when treatment was extended to 10 days (Table 1).

Table 4 Antagonism of tetralin dyskinesias following oral administration, daily for 5 days, of dihomo-γ-linolenic acid (DHLA) to the guinea-pig

Dose of DHLA (mg kg^{-1} orally)	*Tetralin dyskinesias* (mean score ± s.e.mean $n=6$)
Vehicle	2.8 ± 0.06
50	2.0 ± 0.12*
100	0.7 ± 0.06**
200	0.2 ± 0.07**

Reductions in dyskinesia responding by DHLA significant to *$P<0.05$, **$P<0.001$ (one-way ANOVA followed by Dunnett's test for multiple comparisons).

The antidyskinetic action of DHLA, either against the dopamine or tetralin dyskinesias, was antagonized by aspirin, or ETYA, 100 mg kg^{-1} i.p. daily, given during a 5 day DHLA treatment and for 2 days prior to DHLA (Tables 2 and 3). Preliminary studies showed the aspirin and ETYA treatments to be less effective when started only one day before the DHLA (possibly reflecting the less complete inhibition of cyclo-oxygenase/lipoxygenase enzyme activity). The aspirin and ETYA treatments alone failed to modify the dyskinesias induced by 100–200 μg dopamine injected into the striatum or 0.0125–0.025 mg kg^{-1} s.c. tetralin (all values at the lowest doses of dopamine and tetralin were within the range 1.3 ± 0.10 to 1.4 ± 0.09).

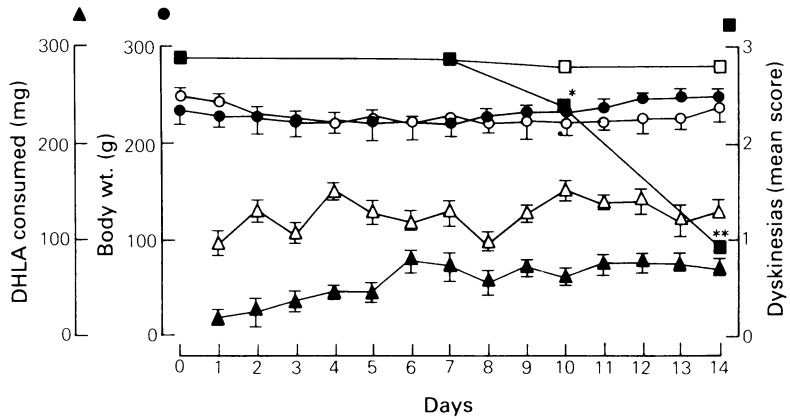

Figure 1 Antagonism of dyskinesias by dihomo-γ-linolenic acid (DHLA) given in the diet of rats. Control animals were given palmitic acid in their diet; (■) mean tetralin dyskinesia score for animals taking DHLA or (□) palmitic acid; (●) body weight (g) of animals receiving DHLA or (○) palmitic acid; (▲) amount of DHLA and (△) palmitic acid taken per rat in 24 h (mg). $n = 5$, s.e.means given. Significant reductions in tetralin dyskinesias by DHLA from control values are indicated as $*P < 0.01$; $**P < 0.001$ (Student's t test).

Antagonism of dyskinesias by DHLA administered orally to the guinea-pig

DHLA administered orally for 5 days (50–200 mg kg^{-1}) was shown to antagonize the dyskinetic action of tetralin in the guinea-pig, 100 and 200 mg kg^{-1} DHLA being particularly effective (Table 4).

Antagonism of dyskinesias by DHLA administered in the diet of the rat

Rats fed diet containing DHLA increased their consumption over the first 6 day period to a maximum intake of DHLA of approximately 200 mg kg^{-1} daily. This intake was maintained over the subsequent 8 day period. Although body weight decreased slightly over the first 10 days of treatment and was increasing more slowly than might be expected by the termination of the experiment on day 13, the animals remained healthy throughout and showed normal weight gain when returned to their standard stock cages and diet. The consistent intake of DHLA in the diet was sufficient to reduce significantly the intensity of tetralin dyskinesias by the 10th day and, more markedly, by the 14th day (Figure 1). Animals given palmitic acid in their diet ('controls' to provide free fatty acid) consumed a maximum of 500 mg kg^{-1} daily; the weight loss and subsequent gain towards the end of the 14 day period followed that recorded for rats given the DHLA diet. However, in contrast to DHLA, the intake of palmitic acid failed to modify the tetralin-induced dyskinesias (Figure 1).

Antagonism of dyskinesias by DHLA injected into the striatum of the rat: modification by aspirin

The immediate effects of injecting DHLA into the striatum were the development of a repetitive sniffing with increased exploration followed after 15 to 30 min by periods of intense grooming. These effects, apparent on the 1st to 4th days of injection, were not apparent following intrastriatal injection of vehicle. DHLA injected into the striatum failed to cause any

Table 5 Antagonism of tetralin dyskinesias by dihomo-γ-linolenic acid (DHLA) given daily into the striatum of rats

Day of injection	*Dose of DHLA* (μg)	*Volume of DHLA* (μl)	*Tetralin dyskinesias* (mean score ± s.e. mean $n = 6$)
1	20	2	2.0 ± 0.09*
2	20	2	0.8 ± 0.03*
3	20	2	0.8 ± 0.04*
4	20	2	1.2 ± 0.07*
1, 2, 3, 4	Vehicle	2	2.8 ± 0.11
2	1.25	1	2.4 ± 0.34
2	2.5	1	1.6 ± 0.17*
2	5	2	1.4 ± 0.13*
2	10	1	1.2 ± 0.18*
2	20	2	0.8 ± 0.09*
2	Vehicle	1	2.9 ± 0.03

Significant reductions in tetralin dyskinesias by DHLA indicated as $*P < 0.001$ (one-way ANOVA followed by Dunnett's test for multiple comparisons).

Table 6 Antagonism by aspirin of the antidyskinetic action of intrastriatal dihomo-γ-linolenic acid (DHLA) in the rat

Dose of aspirin (mg kg^{-1} i.p.)	*Dose of DHLA* (μg)	*Tetralin dyskinesias* (mean score ± s.e.mean $n=6$)
Vehicle	5	1.5 ± 0.21
25	5	2.0 ± 0.22
50	5	2.8 ± 0.18*
100	5	3.0 ± 0.0*
Vehicle	20	1.0 ± 0.08
25	20	1.2 ± 0.13
50	20	1.9 ± 0.16*
100	20	2.3 ± 0.16*

Significant antagonism by aspirin of the antidyskinetic effect of DHLA significant to $*P<0.001$ (one-way ANOVA followed by Dunnett's test for multiple comparisons).

motor depression or catalepsy, and by 1 h after injection when tetralin was given s.c., animals appeared alert but with no apparent change in locomotor responding. On the first day of injection, intrastriatal DHLA caused an approximate 30% reduction of the tetralin dyskinesias; this increased to a maximum of an approximate 60% reduction on day 2 (Table 5). The antidyskinetic action of DHLA in the striatum was dose-related, and was antagonized by aspirin in a dose-related manner (Table 6).

Failure of DHLA, administered intraperitoneally or in the diet, to modify apomorphine-induced stereotyped behaviour or haloperidol-induced catalepsy in the rat

Apomorphine (0.25–2.0 mg kg^{-1} s.c.) induced dose-related stereotyped sniffing and biting responses, and haloperidol (0.25–2.0 mg kg^{-1} i.p.) caused dose-related catalepsy in the rat. The stereotyped behaviour induced by 0.5 or 2.0 mg kg^{-1} s.c. apomorphine and the catalepsy induced by 0.25 or 1.0 mg kg^{-1} haloperidol (moderate or marked responses) were neither reduced nor enhanced by DHLA given daily for 10 days by the i.p. route at the high dosage of 100 mg kg^{-1}, or by DHLA taken in the diet for 14 days at a dose of approximately 200 mg kg^{-1} daily (Table 7). Furthermore, in none of the studies reported here, did any dose of DHLA cause catalepsy on its own.

Discussion

Dihomo-γ-linolenic acid (DHLA) is one of the naturally occurring long chain polyunsaturated fatty acids which, esterified in phospholipids, play an important role in determining the structural and functional properties of membranes. In addition, DHLA is an essential fatty acid, the precursor of the prostaglandin 1 series and, through desaturation to arachidonic acid, a precursor of the prostaglandin 2 series (Van Dorp, 1971).

The present studies used 2 models of dyskinesias in

Table 7 The failure of dihomo-γ-linolenic acid (DHLA), administered intraperitoneally or in the diet, to modify apomorphine-induced stereotyped behaviour or haloperidol-induced catalepsy in the rat

Apomorphine (mg kg^{-1} s.c.)	*Haloperidol* (mg kg^{-1} i.p.)	*DHLA* (mg kg^{-1})	*Stereotyped behaviour* (mean score ± s.e. mean $n=6$–12)	*Catalepsy* (mean score ± s.e. mean $n=12$)
0.25			1.2 ± 0.1	
0.5			2.2 ± 0.2	
1.0			3.0 ± 0	
2.0			4.0 ± 0	
0.5		100 (i.p. 10 days)	2.0 ± 0	
2.0		100 (i.p. 10 days)	4.0 ± 0	
0.5		200 (p.o. 14 days)	2.3 ± 0.2	
2.0		200 (p.o. 14 days)	4.0 ± 0	
	0.25			1.0 ± 0
	0.5			2.5 ± 0.2
	1.0			3.8 ± 0.4
	2.0			5.0 ± 0
	0.5	100 (i.p. 10 days)		2.5 ± 0.2
	2.0	100 (i.p. 10 days)		5.0 ± 0
	0.5	200 (p.o. 14 days)		2.6 ± 0.3
	2.0	200 (p.o. 14 days)		5.0 ± 0

the rodent, the perioral movements induced by dopamine injected into the striatum of the guinea-pig and by 2-di-*n*-propylamino-5, 6-dihydroxytetralin in the guinea-pig and rat. The perioral movements seen after dopamine injection into the striatum are specifically induced by dopamine agonists, and were initiated from an area of the striatum previously identified as being particularly sensitive to mediate these effects (Costall *et al.*, 1975; 1980b). The striatum can also mediate the perioral movements caused by peripherally administered tetralin (Costall *et al.*, 1977), since the injection of tetralin into the striatum induces perioral movements (Costall *et al.*, 1980a).

The value of the models of perioral movements induced by dopamine and tetralin lies in their sensitivity to antagonism by agents known to exert antidyskinetic activity in the clinic whilst they are relatively insensitive to other neuroleptic agents. Thus the number of effective antidyskinetic agents revealed by the use of the dopamine and tetralin models has been small and only two agents, oxiperomide and tiapride, have been tested clinically, where their antidyskinetic action has been confirmed (Lhermitte *et al.*, 1977; Bédard *et al.*, 1978; Price *et al.*, 1978; Buruma *et al.*, 1982). The ability of a potential antidyskinetic agent to antagonize the dopamine-induced dyskinesias is a particularly stringent test, and even a potent dopamine antagonist, for example haloperidol, and compounds such as metoclopramide and sulpiride fail to antagonize the intense dopamine receptor stimulation caused by dopamine injection into the striatum, and these agents are only effectively 'antidyskinetic' at higher doses in the tetralin model (Costall & Naylor, 1975; unpublished data). Nevertheless, these agents may exert some antidyskinetic actions in the clinic, even though this may be complicated by other extrapyramidal disturbance (Casey *et al.*, 1979; Doongaji *et al.*, 1979).

Thus, the demonstration in the present studies that a further agent DHLA, unrelated to the neuroleptic drugs and demonstrating no classical neuroleptic-like activities in animals (Holmes, personal communication), exerts antidyskinetic activity assumes particular interest in an area where drug therapy is limited.

DHLA was shown to exert a specific antidyskinetic action in both the rat and guinea-pig. Dyskinesias could be effectively reduced or abolished by DHLA given intraperitoneally, orally or (to demonstrate a central action) directly into the brain area thought to control dyskinesia responding, the striatum (Costall *et al.*, 1980a). In each situation the effectiveness of DHLA was revealed by repeated daily dosing, maximum efficacy being recorded after 5 to 10 days of oral or systemic treatment, dependent on the dose, or after 2 daily injections directly into the striatum. Even DHLA taken in the diet for 10 to 14 days was shown to antagonize the dyskinesias.

The specificity of the antidyskinetic activity of DHLA was demonstrated by its inability to induce or modify other behavioural paradigms of striatal dopamine dysfunction. Thus, repeated treatment with DHLA failed to induce catalepsy, failed to antagonize apomorphine stereotypy and failed to modify the cataleptic actions of haloperidol. The findings also indicate an unusual mechanism for the antidyskinetic action of DHLA (or its products). Other antidyskinetic agents, oxiperomide and tiapride, exert an action most reasonably attributed to a direct blockade of striatal dopamine receptors. In contrast, we would suggest that the antidyskinetic action of DHLA may relate to its incorporation into lipid membranes and conversion to prostaglandins. The need for repeated treatment is consistent with its acting as a precursor, as is the prevention of the antidyskinetic action by treatment with aspirin and ETYA. Aspirin inhibits cyclo-oxygenase enzymes and ETYA inhibits both cyclo-oxygenase and lipoxygenase enzymes essential for the formation of prostaglandins and leukotrienes (Higgs & Vane, 1983).

It is therefore of interest that the injection of prostaglandin E_2 (PGE_2) and PGD_2 into the striatum have been shown to modify amphetamine-induced circling (a behaviour mediated via striatal dopamine) of the mouse. The sum total of such data suggest that DHLA may, at least in part, exert its antidyskinetic action through the formation of prostaglandins (Schwarz *et al.*, 1982).

DHLA may be useful as a novel antidyskinetic agent. If this action is via mechanism(s) closely linked with prostaglandin function in the striatum and not by direct interaction with striatal dopamine receptors, then the extrapyramidal side effects associated with high dosage neuroleptic therapy, the usual approach to dyskinesia control, may not present as a complicating factor of DHLA treatment.

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References

BALDESSARINI, R.J., COLE, J.O., DAVIS, J.M., PRESKORN, S.H., SIMPSON, G.M. & TARSY, D. (1979). *Tardive Dyskinesia.* Report of the American Psychiatric Association Task Force on Late Neurological Effects of Antipsychotic Drugs. Washington: American Psychiatric Association.

BÉDARD, P., PARKES, J.D. & MARSDEN, C.D. (1978). Effect of new dopamine-blocking agent (oxiperomide) on

drug-induced dyskinesias in Parkinson's disease and spontaneous dyskinesias. *Br. med. J.*, **i,** 954–956.

BURUMA, O.J.S., ROOS, R.A.C., BRUYN, G.W., KEMP, B, & VAN DER VELDE, E.A. (1982). Tiapride in the treatment of tardive dyskinesia. *Acta Neurol. scand.*, **65,** 38–44.

CASEY, D.E., GERLACH, J. & SIMMELSGAARD, H. (1979). Sulpiride in tardive dyskinesia. *Psychopharmacology*, **66,** 73–77.

COSTALL, B., DE SOUZA, C.X. & NAYLOR, R.J. (1980a). Topographical analysis of the actions of 2-(N,N-dipropyl) amino-5, 6-dihydroxytetralin to cause biting behaviour and locomotor hyperactivity from the striatum of the guinea-pig. *Neuropharmacology*, **19,** 623–631.

COSTALL, B., DE SOUZA, C.X. & NAYLOR, R.J. (1980b). Dopamine receptors mediating different motor responses may have differential topography in the guinea-pig striatum. *Br. J. Pharmac.*, **70,** 148P.

COSTALL, B. & NAYLOR, R.J. (1975). Neuroleptic antagonism of dyskinetic phenomena. *Eur. J. Pharmac.*, **33,** 301–312.

COSTALL, B., NAYLOR, R.J. & OWEN, R.T. (1977). Investigation into the nature of the peri-oral movements induced by 2-(N,N-dipropyl)amino-5, 6-dihydroxytetralin. *Eur. J. Pharmac.*, **45,** 357–367.

COSTALL, B., NAYLOR, R.J. & PINDER, R.M. (1975). Dyskinetic phenomena caused by the intrastriatal injection of phenylethylamine, phenylpiperazine, tetrahydrosioquinoline and tetrahydronaphthalene derivatives in the guinea-pig. *Eur. J. Pharmac.*, **31,** 94–109.

DE GROOT, J. (1959). The rat forebrain in stereotaxic coordinates. *Verh. K. Ned. Akad. Wet.*, **52,** 14–39.

DOONGAJI, D.R., JESTE, D.V., JAPE, N.M., SHETH, A.S., APTE, J.S., VAHIA, V.N., DESAI, A.B., PARIKH, M.D., RATHI, L.G., GHANDI, M.H., PARIKH, R.M., THATTE, S. & BHARADWAJ, J. (1982). Effects of intravenous metoclopramide in 81 patients with tardive dyskinesia. *J. clin. Psychopharmac.*, **2,** 376–379.

GERLACH, J. (1979). Tardive dyskinesia. *Dan. med. Bull.*, **26,** 209–245.

GOETZ, C.G. (1983). Diagnosis of tardive dyskinesia. *Clin. Neuropharmac.*, **6,** 101–107.

HIGGS, G.A. & VANE, J.R. (1983). Inhibition of cyclo-oxygenase and lipoxygenase. *Br. med. Bull.*, **39,** 265–270.

JESTE, D.V. & WYATT, R.J. (1982). Therapeutic strategies against tardive dyskinesias: two decades of experience. *Am. J. Psychiat.*, **39,** 803–816.

KANE, J.M. & SMITH, J.M. (1982). Tardive dyskinesias: prevalence and risk factors, 1959–1979. *Arch. gen. Psychiat.*, **39,** 473–481.

KARSON, C.N., JESTE, D.V., LEWITT, P.A. & WYATT, R.J. (1983). A comparison of two iatrogenic dyskinesias. *Am. J. Psychiat.*, **140,** 1504–1506.

LHERMITTE, F., AGID, Y., SIGNORET, J. -L. & STUDLER, J. -M. (1977). Les dyskinesies de << début et fin de dose >> provoquees par la l-dopa. *Rev. Neurol.*, (Paris), **133,** 297–308.

PRICE, P., PARKES, J.D. & MARSDEN, C.D. (1978). Tiapride in Parkinson's disease. *Lancet*, **i,** 1106.

SCHWARZ, R.D., URETSKY, N.J. & BIANCHINE, J.R. (1982). Prostaglandin inhibition of amphetamine-induced circling in mice. *Psychopharmacology*, **78,** 317–321.

SIMPSON, G.M., PI, E.H. & SRAMEK, J.J. (1982). Management of tardive dyskinesia: current update. *Drugs*, **23,** 381–393.

VAN DORP, D.A. (1971). Recent developments in the biosynthesis and analysis of prostaglandins. *Ann. N.Y. Acad. Sci.*, **180,** 181–199.

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