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Modification of dyskinesias following the intrastriatal injection of prostaglandins in the rodent

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1 The abilities of prostaglandin E_1 (PGE_1), PGE_2, PGD_2 and $PGF_{2\alpha}$ to antagonize striatal dopamine function were assessed following bilateral and unilateral injections into the striata of the rat and guinea-pig.

2 Three tests were used to assess the effects of the bilateral injections, ability to antagonize dyskinetic biting induced by 2-di-*n*-propylamino-5, 6-dihydroxytetralin (0.025 mg kg^{-1} s.c.), ability to antagonize stereotyped behaviour induced by apomorphine (0.5 or 2 mg kg^{-1} s.c.) and ability to induce catalepsy. Asymmetry/circling behaviour revealed on challenge with apomorphine (0.25 mg kg^{-1} s.c.) was measured following unilateral injection into the striatum.

3 In the rat, dyskinetic biting induced by 2-di-*n*-propylamino-5, 6-dihydroxytetralin was antagonized by PGE_1 (0.001–1 μg) and PGE_2 (0.00001–1 μg) but not by PGD_2 or $PGF_{2\alpha}$ (1 μg). Stereotyped behaviour induced by apomorphine was not antagonized by any of the prostaglandins. A weak catalepsy was induced by PGE_1 (1 μg only), PGE_2 (0.001–1 μg) and PGD_2 (0.001–1 μg) but not by $PGF_{2\alpha}$. Asymmetry and circling behaviour was only observed following the unilateral injection into the striatum of PGE_1 and PGD_2 (0.01–1 μg) and challenge with apomorphine.

4 In the guinea-pig the actions of PGE_1 and E_2 were compared with those of $PGF_{2\alpha}$. Dyskinetic biting induced by 2-di-*n*-propylamino-5, 6-dihydroxytetralin was antagonized by bilateral injections into the striatum of PGE_2 (0.001–1 μg), but not PGE_1 (0.5 μg) and $PGF_{2\alpha}$ (1 μg) but not PGE, (0.5 μg) and $PGF_{2\alpha}$ (1μg). Similar injections of PGE_1, E_2 and $F_{2\alpha}$ all failed to antagonize apomorphine-induced stereotyped behaviour, or to induce catalepsy. PGE_1 (0.01–0.5 μg) and PGE_2 (0.002–1 μg), but not $PGF_{2\alpha}$, caused asymmetry following unilateral injection into the striatum and peripheral challenge with apomorphine.

5 It is concluded that the major effect in the striatum of the prostaglandins of the E series is to antagonize dyskinetic biting; this action is not shared by other prostaglandins tested, and does not reflect a generalised ability to antagonize striatal dopamine function. It is suggested that the actions of the prostaglandins to modify differentially dopamine-dependent behaviours from the striatum may reflect activity at a site subsequent to the dopamine receptor.

Introduction

The dyskinetic biting induced by the intrastriatal injection of dopamine or the peripheral administration of the dopamine agonist 2-di-*n*-propylamino-5, 6--dihydroxytetralin in the rodent is antagonized by subchronic treatment with dihomo-γ-linolenic acid (Costall *et al.*, 1984a). The essential fatty acid, dihomo-γ-linolenic acid, is the immediate precursor of the 1 series prostaglandins and, through desaturation to arachidonic acid, is a precursor of the 2 series prostaglandins (Van Dorp, 1971). The formation of the prostaglandins from dihomo-γ-linolenic acid is dependent on cyclo-oxygenase, an enzyme that can be inhibited by aspirin and eicosa-5, 8, 11, 14-tetraynoic acid (Higgs & Vane, 1983). Pretreatment with the latter agents can prevent the antidyskinetic actions of dihomo-γ-linolenic acid which would suggest that its actions are mediated via the formation of prostaglandins (Costall *et al.*, 1984a).

Although prostaglandins are known to occur in the central nervous system where they may exert a number of effects (Holmes & Horton, 1968; Wolfe, 1975; Wolfe & Coceani, 1979) a physiological role in the control of motor function has not been shown. It has been shown that after intracerebroventricular injection prostaglandins are able to induce catalepsy (Horton, 1964), potentiate or reduce neuroleptic

catalepsy (see Brus *et al.*, 1983), antagonize conditioned avoidance responding (Potts *et al.*, 1973) and mouse climbing behaviour (Brus *et al.*, 1982), effects similar to those produced by dopamine receptor antagonists and which may indicate an inhibitory action on dopamine neurotransmission.

The present investigation of the antidyskinetic actions of prostaglandins involved injection directly into the striatum as a site of dyskinesia induction, to avoid the problems of penetration of prostaglandins into the brain following peripheral injections (and the peripheral actions of such treatments) or the lack of locus specificity of action that is achieved following intracerebroventricular injection. Preliminary findings of part of this work have been presented to the British Pharmacological Society (Costall *et al.*, 1984b).

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.

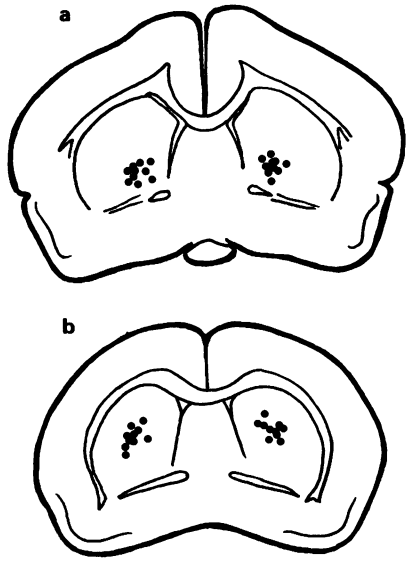

Figure 1 Diagrammatic representation of the injection sites (●) in (a) the ventromedial neostriatal complex of the guinea-pig and (b) the centre of the neostriatal complex of the rat. The diagrams were constructed from data obtained from the brains of 10 guinea-pigs and 10 rats.

Stereotaxic surgery and intrastriatal injection technique

Standard stereotaxic techniques were applied for the implantation of chronically indwelling guide cannulae to allow subsequent drug or vehicle injection into the centre of the neostriatal complex of the rat (Ant. 7.8, Vert. + 1.0, Lat. ± 3.0, De Groot, 1959) or into the ventromedial striatum of the guinea-pig (Ant. 8.0, Vert. + 4.1, Lat. ± 3.5, Costall *et al.*, 1980) (see Figure 1). Guide cannulae were made from 0.65 mm external diameter stainless steel tubing held bilaterally in perspex blocks. They were implanted with their tips 2.0 mm above the selected injection points and kept patent by stainless steel stylets (0.3 mm external diameter) which were only removed to allow the insertion of the injection units (0.3 mm external diameter). Animals were used for intracerebral injection after a 14 day recovery period when they were manually restrained and drug or vehicle injected in a volume of 1 μl over a 5 s period with 55 s allowed for drug deposition. Injections were made bilaterally or unilaterally using Agla micrometer syringes. On withdrawal of the injection units the stylets were replaced and the rats and guinea-pigs placed in individual observation cages for behavioural assessment.

Behavioural tests

Rats and guinea-pigs were normally housed in groups of 3 to 5. For visual assessment of behaviour (between 10 h 30 min and 16 h 30 min) they were placed in individual perspex cages measuring 25 × 14 × 14 cm (unless otherwise stated). Separate cages of the same dimensions but fitted with a 10 cm high perspex bar were used for catalepsy assessment. Experiments were carried out in a diffusely illuminated, sound-proofed room maintained at 21–23°C.

Dyskinetic biting was induced in guinea-pigs and rats by 2-di-*n*-propylamino-5, 6-dihydroxytetralin. Intensity was scored by observation over a 30 s period and allocating a score of 1 to a weak response in which an animal demonstrated occasional dyskinetic biting behaviour, score 2 to a moderate intensity response in which the periods of biting were dominant but clearly broken by brief periods when biting was absent, and score 3 to an intense response where the dyskinetic biting was continuous (see Costall *et al.*, 1984a). Initial studies assessed the effects of 0.00625–0.5 mg kg^{-1} s.c. 2-di-*n*-propylamino-5, 6-dihydroxytetralin in the rat and guinea-pig and 0.025 mg kg^{-1} was selected as the lowest dose causing a dyskinetic biting of score 3 in all animals. Prostaglandin E_1 (PGE_1,), PGE_2, and $PGF_{2\alpha}$ or their vehicles, were injected bilaterally into the striata of rat and guinea-pig 20 min before the administration of 2-di-*n*-propylamino-5, 6-dihydroxy-

tetralin. Modification of dyskinetic biting was determined by measuring biting at 5 min intervals from onset (20 min) for 45 min. The mean score for dyskinetic biting was determined for each animal and then for each group of animals.

Stereotyped behaviour was induced in the rat by apomorphine. Intensity was scored over a 30 s period by allocating score 1 for discontinuous sniffing and/or repetitive head and limb movements, score 2 for continuous sniffing and/or repetitive head and limb movements, score 3 for periodic biting or licking, and score 4 for continuous biting or licking. Initial studies assessed the stereotypic effects of 0.25–2.0 mg kg^{-1} s.c. apomorphine and 0.5 and 2.0 mg kg^{-1} were selected as the lowest doses causing a score 4 stereotypy in the rat and guinea-pig respectively. PGE_1, E_2, D_2 and $F_{2\alpha}$, or their vehicles, were injected bilaterally into the striata of rat or guinea-pig 20 min before the administration of apomorphine. Stereotyped behaviour was then assessed at 10 min intervals from onset (15 min) and the mean maximum score determined for each group of animals.

Asymmetric behaviour Ability to induce this behaviour following unilateral intrastriatal administration was assessed by scoring this behaviour 0–3, where 0 = no asymmetry, response the same as that of untreated animals, 1 = a distinct tendency for animals to move in one direction only when handled but still capable of movement in either direction, 2 = spontaneous movements in one direction, a twisting of the body in this direction, exaggerated when handled, with inability to move in the opposite direction, 3 = animal showing marked and persistent spontaneous twisting of the body in one direction only, nose to tail, animal unable to move in opposite direction. For observation, animals were placed in 'open fields', 40 cm wide, immediately after the intrastriatal injection of PGE_1, E_2, D_2 and $F_{2\alpha}$ or their vehicle. Spontaneous movements were recorded for 20 min and then 0.25 mg kg^{-1} s.c. apomorphine was administered to reveal any asymmetry by an action in the 'intact' hemisphere (see Costall *et al.*, 1983).

Circling behaviour Throughout these experiments any active circling behaviour was measured in revolutions per minute, an animal being categorised as an active circler only when it moved in one direction only.

Catalepsy assessment The ability of bilateral intrastriatal administration of PGE_1, E_2, D_2 or $F_{2\alpha}$ (with vehicle controls) to induce a cataleptic state in the rat or guinea-pig was assessed by application of a scoring system which allows the demonstration of a dose-dependency for the cataleptic action of haloperidol (0.25–2.0 mg kg^{-1} i.p. gave scores ranging from 1–5). Catalepsy was measured by carefully placing an animal 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 10–30 min after drug administration and the catalepsy scored as follows: 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.

Drugs

PGE_1, E_2, D_2 and $F_{2\alpha}$ (Sigma) were prepared for intrastriatal injection in distilled water, N_2 bubbled. Apomorphine HCl (Sigma) and 2-di-*n*-propylamino-5, 6-dihydroxytetralin HCl (Glaxo) were prepared in a 0.1% solution of sodium metabisulphite and haloperidol (Janssen) in 1% lactic acid.

Table 1 Effects of prostaglandins administered bilaterally into the striatum of rats on the dyskinetic biting induced by peripherally administered 2-di-*n*-propylamino-5, 6-dihydroxytetralin

Dose of prostaglandins (μg)	*Dyskinesias* (mean score) E_1	E_2	D_2	$F_{2\alpha}$
Vehicle	3.0 ± 0.0	2.8 ± 0.07	3.0 ± 0.0	2.9 ± 0.03
1.0	0.7 ± 0.07*	0.4 ± 0.06*	2.7 ± 0.08	2.6 ± 0.07
0.1	0.5 ± 0.08*	0.3 ± 0.04*	2.9 ± 0.03	2.4 ± 0.08
0.01	1.0 ± 0.12*	0.3 ± 0.03*	3.0 ± 0.0	2.6 ± 0.07
0.001	1.2 ± 0.15*	0.5 ± 0.05*	3.0 ± 0.0	3.0 ± 0.0
0.0001	2.5 ± 0.28	1.3 ± 0.21*	2.8 ± 0.03	3.0 ± 0.0
0.00001	2.9 ± 0.05	1.6 ± 0.17*	2.9 ± 0.08	2.9 ± 0.04
0.000001	2.8 ± 0.08	2.5 ± 0.08	3.0 ± 0.0	2.8 ± 0.03

$n = 6–12$; s.e.means given. Significant reductions from vehicle control values are indicated as $*P < 0.05 - P < 0.001$ (Mann Whitney U-test).

Table 2 The ability of intrastriatally administered prostaglandins to cause catalepsy but not to antagonize sterotypy induced by apomorphine (0.5 mg kg^{-1}, s.c.) in the rat

Dose of prostaglandins	*Catalepsy* (mean score)				*Stereotypy* (mean score)			
	E_1	E_2	D_2	$F_{2\alpha}$	E_1	E_2	D_2	$F_{2\alpha}$
1.0	0.8 ± 0.7*	1.0 ± 0.0**	1.0 ± 0.00**	0.0	4.0 ± 0.0	4.0 ± 0.0	3.8 ± 0.03	4.0 ± 0.0
0.1	0.0	0.6 ± 0.07*	1.0 ± 0.00**	0.0	3.6 ± 0.07	4.0 ± 0.0	3.8 ± 0.04	4.0 ± 0.0
0.01	0.0	0.8 ± 0.06*	0.8 ± 0.06*	0.0	4.0 ± 0.0	3.8 ± 0.06	4.0 ± 0.0	3.9 ± 0.03
0.001	0.0	0.6 ± 0.06*	0.8 ± 0.07*	0.0	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0
0.0001	—	0.7 ± 0.09*	0.5 ± 0.05*	—	—	—	—	—
0.00001	—	0.3 ± 0.02*	0.0	—	—	—	—	—
0.000001	—	0.0	0.0	—	—	—	—	—

$n = 4-12$; s.e.means given. Production of catalepsy significant to *$P < 0.05$; **$P < 0.001$ (comparison to responses of vehicle-treated animals, Mann Whitney U-test).

Table 3 The development of ipsilateral asymmetric and circling behaviour in the rat following unilateral intrastriatal injection of prostaglandins and challenge with apomorphine (0.25 mg kg^{-1}, s.c.)

Dose of prostaglandins (μg)	*Asymmetry* (mean score)				*Circling* (mean rev min^{-1})			
	E_1	E_2	D_2	$F_{2\alpha}$	E_1	E_2	D_2	$F_{2\alpha}$
1.0	3.0 ± 0.0**	0.0	2.8 ± 0.1**	0.0	4.3 ± 0.5**	0.0	5.4 ± 0.6**	0.0
0.1	2.5 ± 0.3**	0.0	2.2 ± 0.2**	0.0	3.1 ± 0.3**	0.0	2.6 ± 0.3**	0.0
0.01	2.1 ± 0.2**	0.0	0.9 ± 0.1*	0.0	1.7 ± 0.2*	0.0	1.4 ± 0.2*	0.0
0.001	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.0001	0.0	—	0.0	—	0.0	—	0.0	—
0.00001	—	—	—	—	—	—	—	—
0.000001	—	—	—	—	—	—	—	—

$n = 4-12$; s.e.means given. Production of asymmetry or circling significant to *$P < 0.05$, **$P < 0.01-P < 0.001$ (comparison to responses of vehicle-treated animals, Mann Whitney U-test).

Results

Both PGE_1 (0.001 – 1 μg) and E_2 (0.00001 – 1 μg) injected bilaterally into rat striata dose-dependently antagonized the dyskinetic biting induced by peripherally administered 2-di-*n*-propylamino-5, 6-dihydroxytetralin. PGE_2 was approximately 100 fold more potent in this respect than PGE_1 (Table 1). In contrast, doses of PGD_2 and $F_{2\alpha}$ up to 1 μg injected bilaterally into rat striata failed to modify significantly the response to 2-di-*n*-propylamino-5, 6-dihydroxytetralin (Table 1). PGE_1, E_2, and $F_{2\alpha}$, at doses up to 1 μg, injected bilaterally into the striata failed to modify the stereotyped behaviour patterns induced by 0.5 mg kg^{-1} s.c. apomorphine (Table 2). However, the higher doses of PGE_1 and D_2 (0.01 – 1 μg) injected unilaterally into the striatum were shown to induce asymmetry and circling behaviour but this was only revealed on apomorphine administration (Table 3). In contrast, PGE_2 and $F_{2\alpha}$, at doses up to 1 μg, failed to cause any asymmetry or circling behaviour, either spontaneously or on apomorphine challenge, follow-

Table 4 Effects of prostaglandins administered bilaterally into the striatum of guinea-pigs on the dyskinetic biting induced by peripherally administered 2-di-*n*-propylamino-5,6-dihydroxytetralin (0.025 mg kg^{-1}, s.c.)

Dose of prostaglandins (μg)	*Dyskinesias* (mean score)		
	E_1	E_2	$F_{2\alpha}$
Vehicle	2.9 ± 0.03	2.9 ± 0.03	2.9 ± 0.03
1.0	—	0.6 ± 0.05*	3.0 ± 0.0
0.5	2.4 ± 0.08	—	—
0.1	2.8 ± 0.22	1.0 ± 0.17*	2.9 ± 0.03
0.01	2.9 ± 0.09	0.8 ± 0.02*	—
0.001	2.8 ± 0.08	2.4 ± 0.08	—
0.0001	2.9 ± 0.03	2.9 ± 0.03	—

$n = 5-10$; s.e.means given. Significant reductions from vehicle control values indicated as *$P < 0.01-P < 0.001$ (Mann Whitney U-test).

Table 5 Ability of prostaglandins to induce asymmetry (on challenge with apomorphine 0.25 mg kg^{-1}, s.c.) when injected unilaterally into guinea-pig striatum, but not to cause catalepsy or antagonize stereotypy (induced by apomorphine 2 mg kg^{-1}, s.c.) when injected bilaterally into guinea-pig striatum

Prostaglandin	*Intrastriatal dose (μg)*	*Stereotypy* (mean score)	*Catalepsy* (mean score)	*Asymmetry* (mean score)
PGE_1	Vehicle	3.8 ± 0.1	0.0	0.0
	0.5	3.6 ± 0.08	0.0	2.2 ± 0.28**
	0.1	4.0 ± 0.0	0.0	1.1 ± 0.14*
	0.01	3.8 ± 0.03	0.0	0.9 ± 0.10
	0.001	3.9 ± 0.03	0.0	0.4 ± 0.05
	0.0001	4.0 ± 0.0	—	0.0
PGE_2	Vehicle	4.0 ± 0.0	0.0	0.0
	1.0	3.8 ± 0.04	0.0	2.1 ± 0.3
	0.1	4.0 ± 0.0	0.0	2.0 ± 0.0**
	0.01	3.6 ± 0.04	0.0	1.6 ± 0.2*
	0.001	3.8 ± 0.03	0.0	0.0
	0.0001	3.9 ± 0.03	—	0.0
$PGF_{2\alpha}$	Vehicle	4.0 ± 0.0	0.0	0.0
	1.0	4.0 ± 0.0	0.0	0.0
	0.1	3.8 ± 0.04	0.0	0.0

$n = 5-10$; s.e.means given. Production of asymmetry significant to $*P < 0.05$, $**P < 0.01 - P < 0.001$ (comparison to responses of vehicle-treated animals, Mann Whitney U-test).

ing unilateral intrastriatal injection (Table 3). PGE_1 (1 μg only), E_2 (0.00001 – 1 μg) and D_2 (0.0001 – 1 μg), but not $F_{2\alpha}$ (1 μg), injected bilaterally into the striata were shown to induce a weak cataleptic response (never greater than score 1) (Table 2).

The ability of PGE_2 to antagonize dyskinetic biting induced by 2-di-*n*-propylamino-5, 6-dihydroxytetralin was confirmed in the guinea-pig (Table 4), although the potency in this species was less than that recorded in the rat, and PGE_1, in contrast to the rat, was inactive (Table 4). The intrastriatal administration of $PGF_{2\alpha}$ failed to antagonize dyskinetic biting, to antagonize apomorphine-induced stereotyped behaviour, to induce catalepsy, or to allow the development of asymmetry/circling, either spontaneously or on apomorphine challenge (Tables 4 and 5). PGE_1 and PGE_2 injected bilaterally into the striatum also failed to antagonize apomorphine-induced stereotyped behaviour or to induce catalepsy, although unilateral injections of both PGE_1 (0.001 – 0.5 μg) and PGE_2 (0.01 – 1 μg) caused the development of asymmetries, but these were only revealed on treatment of the guinea-pigs with apomorphine. Active circling behaviour was not observed (Table 4 and 5).

Discussion

2-Di-*n*-propylamino-5, 6-dihydroxytetralin is a potent stimulant of dopamine receptors in many central and peripheral systems (McDermed *et al.*, 1975; Mulder *et al.*, 1980; Goldberg & Kohli, 1981). Its ability to stimulate striatal dopamine receptors leading to orobuccolingual movements, 'dyskinetic biting', which are inhibited by dopamine antagonists provides a useful animal model of abnormal movements (Costall *et al.*, 1980).

In the rat, PGE_1 and E_2 injected into the striatum were potent antagonists of the dyskinetic biting caused by a peripheral treatment with 2-di-*n*-propylamino-5, 6-dihydroxytetralin. PGE_2 was approximately two orders more potent than PGE_1 and the specificity of the antagonism to the E series was shown by the failure of the intrastriatal injection of PGD_2 and $PGF_{2\alpha}$ to antagonize the dyskinetic biting. Assuming that the exogenously applied PGE_1 and PGE_2 are mediating their effects via mechanisms capable of response to endogenous prostaglandins, it is possible that the antidyskinetic actions of the prostaglandins precursor dihomo-γ-linolenic acid, given either peripherally or directly into the striatum (Costall *et al.*, 1984a), are mediated via the production of prostaglandins E. However, although the prostaglandins were shown to block the consequences of dopamine receptor stimulation, it is unlikely that this reflects a dopamine receptor antagonism.

In the present study using the rat, PGE_2, although the most potent agent to antagonize the dyskinetic biting induced by 2-di-*n*-propylamino-5, 6-dihydroxytetralin, failed to induce circling behaviour on unilateral intrastriatal injection, either in its own right or when followed by peripheral apomorphine challenge, failed to antagonize the stereotyped behaviour induced by subcutaneously administered apomorphine and caused only a very low intensity catalepsy on bilateral intrastriatal injection, in contrast to the

positive actions in these tests of the classical dopamine receptor antagonists (Costall *et al.*, 1972; 1983). Schwarz *et al.* (1982) have similarly reported that prostaglandins injected unilaterally into the striatum of mice did not cause circling responses and bilateral injections failed to cause catalepsy or to reduce locomotor activity. It is therefore difficult to interpret the actions of the prostaglandins in terms of a general inhibition of striatal dopamine function. This is further emphasised by the action of PGD_2 which was the most effective of the four prostaglandins examined to induce asymmetry-circling after unilateral intrastriatal injection (in response to apomorphine administered subcutaneously) and catalepsy after bilateral intrastriatal injection, whilst failing to antagonise dyskinetic biting.

The present studies investigating the abilities of prostaglandins to inhibit striatal function in the guinea-pig indicated a similar dissociation of activities. PGE_1, PGE_2 and $PGF_{2\alpha}$ all failed to antagonize apomorphine stereotypy or to induce catalepsy; $PGF_{2\alpha}$ also failed to antagonize the dyskinetic biting induced by 2-di-*n*-propylamino-5, 6-dihydroxytetralin or to cause asymmetry/circling following treatment with apomorphine. Yet PGE_1 and PGE_2 both caused asymmetry/circling and PGE_2 also antagonized dyskinetic biting. Thus, in both the rat and guinea-pig, PGE_2 is shown to be the most potent of the prostaglandins tested to antagonize dyskinetic biting, and such an action does not reflect a general propensity to inhibit striatal dopamine function. It may follow, therefore, that the antidyskinetic action of dihomo-γ-linolenic acid, precursor of prostaglandins, may primarily reflect its conversion to arachidonic acid and hence PGE_2 (Hassam & Crawford, 1978).

Accepting that the prostaglandins may exert differential effects to antagonize striatal dopamine function, the failure of PGE_1, PGE_2, PGD_2 or $PGF_{2\alpha}$ to displace [^{3}H]-spiperone from striatal dopamine receptors in *in vitro* receptor labelling assays (Czlonkowski & Herman, 1980; Holmes, unpublished data) would emphasise that such compounds are not dopamine receptor antagonists. A more indirect action through which the prostaglandins could theoretically modify behaviour is via a change in cerebral circulation. However, this clearly cannot account for (a) the actions of an individual prostaglandin to modify behaviour differentially or (b) differences between prostaglandins since, for example, both PGD_2 and PGE_2 are potent cerebral vasodilators (in the cat) (Ellis *et al.*, 1979) and yet modify behaviour differentially to cause asymmetry/circling or to inhibit dyskinetic biting respectively. It is more prudent to conclude that the abilities of the prostaglandins to inhibit dyskinetic biting differentially, to cause asymmetry/circling or to inhibit apomorphine-induced asymmetries (Schwarz *et al.*, 1982) is due to an action at a site beyond the dopamine receptor, either modulating the process of receptor-transmitter recognition, the immediate events and consequences of receptor stimulation, or events at a more distant site in the neuronal chain.

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