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DIFFERENTIATION OF DOPAMINE AGONISTS USING DRUG-INDUCED ROTATION IN RATS WITH UNILATERAL OR BILATERAL 6-HYDROXYDOPAMINE DESTRUCTION OF ASCENDING DOPAMINE PATHWAYS

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Abstract—Eighteen compounds with dopamine agonist properties were examined in two rat rotational models. In the classical Ungerstedt model, a unilateral 6-hydroxydopamine (6OHDA) lesion destroyed nigrostriatal and mesolimbic dopamine pathways on one side. Indirectly acting compounds, amphetamine, amantadine, methylphenidate and S1694, produced ipsiversive rotation, which was inhibited by pretreatment with α-methyl-*p*-tyrosine (AMPT). All other compounds produced contraversive rotation, but the rotation caused by CM 29-712, bromocriptine and ET 495 was reduced by AMPT. In animals with a bilateral 6OHDA lesion removing both dopaminergic inputs to nucleus accumbens and the dopaminergic input into one striatum, indirectly acting drugs caused ipsiversive posturing prevented by AMPT, but little rotation. All other compounds produced contraversive rotation, but the effects of CM 29-712, bromocriptine and ET 495 were reduced by AMPT pretreatment. Inhibition of monooxygenase drug metabolising activity utilising SKF-525A inhibited contraversive turning induced by bromocriptine and ET 495 in the unilateral lesion model, but had no effect on rotation caused by apomorphine or CM 29-712.

We conclude that, in addition to indirect pre-synaptically acting agonists and direct post-synaptic receptor agonists, there are a small group of compounds which produce rotation associated with direct receptor activation, which is inhibited by disruption of pre-synaptic dopamine function. The mechanism of action of this latter group is not understood, but cannot be attributed solely to active metabolite formation.

Two classes of dopamine agonists are recognised, those acting on post-synaptic receptors, and those acting indirectly by release of pre-synaptically stored dopamine. Directly acting post-synaptic dopamine agonists, such as apomorphine, exert their behavioural effects even if pre-synaptic dopamine mechanisms are destroyed by chemical injury with 6-hydroxydopamine (6OHDA) [1] or by inhibition of dopamine synthesis by α-methyl-*p*-tyrosine (AMPT) [2]. The behavioural effects of indirectly acting pre-synaptic dopamine agonists, such as amphetamine, are prevented by 6OHDA [3] or AMPT [4, 5].

In the classical unilateral 6OHDA lesion model (single-lesion model) [6, 7] directly acting dopamine agonists cause rotation away from the lesioned nigrostriatal pathway due to preferential stimulation of denervated striatal dopamine receptors [1]. Indirectly acting dopamine agonists cause ipsiversive rotation, for they only act by release of dopamine from the opposite intact dopamine pathways. Circling in this situation depends on both a postural deviation due to asymmetrical striatal dopamine action, and locomotor hyperactivity due primarily to stimulation of nucleus accumbens mechanisms [8]. The dopamine pathways to the nucleus accumbens are destroyed on one side by the unilateral 6OHDA lesion, but they remain intact on the opposite side in which indirectly acting dopamine agonists can still release dopamine. If a second 6OHDA lesion is placed at the level of the rostral hypothalamus on the opposite side to the original 6OHDA lesion (double-lesion model), such rats then have a unilateral denervation of one striatum, but bilateral denervation of both nuclei accumbens. Such animals with bilateral lesions still rotate briskly contraversive to the denervated striatum when administered directly acting dopamine agonists, but only posture ipsiversively in response to indirectly acting dopamine agonists, which can no longer produce locomotor drive [9].

Recently many novel dopamine agonist molecules have been introduced and it is clear that the mechanism of action of some may not be by a simple pre- or post-synaptic mechanism. Thus, some dopamine agonists, exemplified by bromocriptine, mimic directly acting agonists in causing contraversive rotation in unilateral 6OHDA-lesioned animals, but their actions resemble those of indirectly acting agonists being inhibited by AMPT [10, 11].

We have examined a total of 18 dopamine agonists for their capacity to cause rotation in unilateral and bilateral 6OHDA-lesioned rats, with and without prior treatment with AMPT. All these drugs were clearly either directly or indirectly acting dopamine agonists, but three compounds (bromocriptine, CM 29-712 and ET 495) appeared to be AMPT-sensitive directly acting dopamine agonists.

MATERIALS AND METHODS

Lesioning techniques. Female Wistar rats [190–230 g (Charles River Ltd)] were anaesthetised using

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chloral hydrate (300 mg/kg i.p.) (BDH) and placed in a Kopf stereotaxic frame. 6OHDA (8 μg in 3 μl 0.9% w/v saline containing 2 μg ascorbic acid) (Sigma Chemical Co.) was focally injected into rats using a 5-μl Hamilton syringe with Luer needle (o.d. 0.33 mm, i.d. 0.18 mm) at a rate of 1 μl/min. Some animals received 6OHDA into the medial forebrain bundle at the level of the left lateral hypothalamus (A + 4.6, L 1.9, V −1.9) (single-lesion model). Other animals received 6OHDA into both the medial forebrain bundle at the level of the left lateral hypothalamus (A + 4.6, L 1.9, V −1.9) and the right rostral hypothalamus (A + 6.6, L 2.3, V −1.0) (double-lesion model). Stereotaxic coordinates were taken from the atlas of De Groot [12]. Some animals underwent sham surgery and received control injections of neurotoxin vehicle at the same coordinates.

Behavioural assessment. Three weeks following surgery animals were assessed for circling behaviour to apomorphine hydrochloride (0.5 mg/kg s.c. 15 min previously) (MacFarlan Smith) or (+)-amphetamine sulphate (3 mg/kg i.p. 30 min previously) (SKF Ltd) during a 1-min observation period at the time of maximal drug effect. Animals with a single 6OHDA lesion were chosen that showed pronounced turning only towards the lesioned side (ipsiversive circling) in response to administration of amphetamine and circling only towards the intact hemisphere (contraversive circling) in response to apomorphine. Animals with the double 6OHDA lesion were selected that showed marked rotation only towards the side of the intact striatum in response to apomorphine, but only postured towards the side of the denervated striatum when administered amphetamine.

Subsequently these groups of animals received a range of dopamine agonists and circling was assessed in a 1-min observation period at the time of maximal response to each compound. Each animal was used on several occasions but at least 2 weeks was allowed between each experimental period and the behaviour of the animals to apomorphine and amphetamine was retested at intervals.

AMPT pretreatment. To assess the contribution of pre-synaptic release of newly synthesised dopamine on the turning produced by the dopamine agonists in the two models, both single and double lesioned animals were pre-treated with AMPT methyl ester hydrochloride (200 mg/kg i.p. AMPT) (Sigma Chemical Co.) or saline (0.1 ml) 1 hr prior to drug administration. The ability of each agonist to induce rotation was then re-examined as previously described.

Inhibition of drug-metabolising enzymes. The actions of four of the dopamine agonists (apomorphine, ET 495, bromocriptine and CM 29-712) also were examined in the single-lesion rotational model after inhibition of monooxygenase drug metabolising enzyme activity by the administration of SKF-525A (75 mg/kg i.p.; proadifen) (SKF Ltd) 30 min prior to the administration of the dopamine agonist. Circling behaviour was examined as described earlier.

Drugs. The following compounds, doses, times of administration prior to assessment of circling and methods of solution were employed: (+)-amphetamine sulphate (3 mg/kg i.p. 30 min prior) (SKF Ltd), amantadine hydrochloride (5 mg/kg i.p. 30 min prior) (Geigy), methylphenidate hydrochloride (10 mg/kg i.p. 30 min prior) (Ciba) and S1694 {[(dihydro - 10,11 - dibenzo[*a,d*]cycloheptenyl - 5)-amino]-7-heptanoic acid hydrochloride} (40 mg/kg i.p. 20 min previously) (Les Laboratoires Servier) were all dissolved in distilled water. Bromocriptine mesylate (10 mg/kg i.p. 30 min prior) (Sandoz Products Ltd), lisuride hydrogen maleate (0.5 mg/kg i.p. 30 min prior) (Schering), ergocriptine maleinate (5 mg/kg i.p. 45 min previously) (Sandoz Products Ltd), ergocornine hydrogen maleinate (5 mg/kg i.p. 30 min prior) (Sandoz Products Ltd) were mixed with an equal quantity of tartaric acid, dissolved in the minimum quantity of 70% ethanol and diluted to vol. with distilled water. Agroclavine (0.05 mg/kg i.p. 30 min previously (Lilly) was dissolved in acidified 0.9% saline and CF-25-397 (9,10-didehydro-6-methyl-8β-(2-pyridylthio-methyl)-ergolene tartrate) (0.5 mg/kg i.p. 30 min prior) (Sandoz Products Ltd) was dissolved in the minimum quantity of *N*-methyl-pyrrolidone and lactic acid and diluted to vol. with distilled water. Elymoclavine (0.025 mg/kg i.p. 30 min prior) (Lilly), lergotrile mesylate (0.25 mg/kg i.p. 15 min prior) (Lilly), apomorphine hydrochloride (0.5 mg/kg s.c. 15 min) (MacFarlan Smith Ltd), SKF 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine hydrochloride) (1.5 mg/kg i.p. 30 min prior) (Smith Kline & French), bromo-LSD (5 mg/kg i.p. 30 min prior) (Sandoz Products Ltd), S3608 [(coumaranyl-5-methyl)-4-(thiazoyl-2)-1-piperazine hydrochloride)] (40 mg/kg i.p. 15 min prior) (Les Laboratoires Servier), CM 29-712 (6-methyl-8α-cyanomethylergolene methane sulphonate) (0.5 mg/kg i.p. 30 min prior) (Sandoz Products Ltd) and ET 495 [4-(piperonyl)-1-(2-pyrimidyl piperazine) methane sulphonate] (40 mg/kg i.p. 20 min prior) (Les Laboratoires Servier) were all dissolved in distilled water.

The dose of each compound administered was determined either by prior assessment or from the literature as being effective for the expression of dopamine agonist activity. In the same manner the times of behavioural assessment employed represent the point of maximal drug effect.

Statistics. Circling rates to dopamine agonists for animals before and after pharmacological manipulation were compared using a two-tailed Student's *t*-test.

RESULTS

Single-lesion model

In animals with a unilateral 6OHDA lesion of the medial forebrain bundle at the level of the left lateral hypothalamus (+)-amphetamine (3 mg/kg i.p.), amantadine (5 mg/kg i.p.), methylphenidate (10 mg/kg i.p.) and S1694 (40 mg/kg i.p.) caused ipsiversive rotation (Table 1). All the other compounds examined caused contraversive rotation (Tables 2 and 3).

AMPT sensitivity of rotation in single-lesion model. Pretreatment of animals with a single 6OHDA lesion with AMPT (200 mg/kp i.p.) 1 hr prior to administration of dopamine agonists abolished the ipsiver-

Table 1. Drugs causing ipsiversive rotation in animals with a unilateral (single) or bilateral (double) 6-hydroxydopamine lesion of the medial forebrain bundle and the effect of pretreatment with AMPT (200 mg/kg i.p. 1 hr previously) on the rate of rotation

Drug	Dose (mg/kg)	Circling (rotations/min)			
		Single lesion		Double lesion	
		Saline	AMPT	Saline	AMPT
Amphetamine	3	9.1 ± 0.8 (7)	0 (7)	1.0 ± 0.5† (8)	0 (8)
Amantadine	5	6.5 ± 1.0 (6)	0 (6)	1.7 ± 0.7† (6)	0 (6)
Methylphenidate	10	7.2 ± 0.8 (6)	0 (6)	2.2 ± 1.0† (6)	0 (6)
S1694	40	8.6 ± 1.6 (5)	3.8 ± 0.6* (5)	3.0 ± 0.7† (9)	1.9 ± 0.6* (9)

Means ± 1 S.E.M. are shown. The values in parentheses indicate the number of animals examined.
* $P < 0.05$ (comparing saline to AMPT).
† $P < 0.05$ (comparing single to double lesion).

sive rotation caused by (+)-amphetamine (3 mg/kg i.p.), amantadine (5 mg/kg i.p.) and methylphenidate (10 mg/kg i.p.), and drastically reduced that caused by S1694 (40 mg/kg i.p.) (Table 1).

The same pretreatment reduced, but did not abolish, the contraversive rotation induced by CM 29-712 (0.5 mg/kg i.p.), bromocriptine (10 mg/kg i.p.) and ET 495 (40 mg/kg i.p.) (Table 3). The contraversive rotation induced by other dopamine agonists was unaffected by this procedure (Table 2).

Double-lesion model

In animals with a 6OHDA lesion both of the medial forebrain bundle at the level of the left lateral hypothalamus and at the level of the right rostral hypothalamus (+)-amphetamine (3 mg/kg i.p.), amantadine (5 mg/kg i.p.), methylphenidate (10 mg/kg i.p.) and S1694 (40 mg/kg i.p.) caused posturing towards the side of the lesioned striatum with occasional rotation (ipsiversive) (Table 1). All other compounds examined caused rotation away from the side of the lesioned striatum (contraversive) (Tables 2 and 3).

AMPT sensitivity of rotation in double-lesion model. Pretreatment of animals with a double 6OHDA lesion with AMPT (200 mg/kg i.p.) 1 hr prior to administration of dopamine agonists abolished the ipsiversive postural and rotational response of animals receiving (+)-amphetamine (3 mg/kg i.p.), amantadine (5 mg/kg i.p.) and methylphenidate (10 mg/kg i.p.) and further reduced that produced by S1694 (40 mg/kg i.p.) (Table 1).

The same pretreatment reduced, but did not abolish, the contraversive rotation induced by administration of CM 29-712 (0.5 mg/kg i.p.), bromocriptine (10 mg/kg i.p.) and ET 495 (40 mg/kg i.p.) (Table 3). The contraversive rotation induced by the other dopamine agonists was unaffected by this procedure (Table 2).

Table 2. Drugs causing contraversive rotation in animals with a unilateral (single) or bilateral (double) 6-hydroxydopamine lesion of the medial forebrain bundle but which are insensitive to the effect of pretreatment with AMPT (200 mg/kg i.p. 1 hr previously)

Drug	Dose (mg/kg)	Circling (rotations/min)			
		Single lesion		Double lesion	
		Saline	AMPT	Saline	AMPT
Elymoclavine	0.025	10.7 ± 1.7 (6)	11.3 ± 1.6 (6)	11.7 ± 3.1 (6)	14.2 ± 2.6 (6)
Agroclavine	0.05	12.7 ± 1.9 (6)	12.5 ± 2.0 (6)	13.3 ± 3.5 (6)	14.8 ± 3.1 (6)
Lergotrile	0.25	18.3 ± 2.5 (6)	17.3 ± 1.7 (6)	16.8 ± 4.4 (6)	16.0 ± 3.3 (6)
Lisuride	0.5	12.3 ± 2.1 (6)	13.2 ± 1.9 (6)	14.6 ± 1.4 (7)	14.2 ± 2.2 (7)
CF-25-397	0.5	12.6 ± 1.8 (5)	13.4 ± 2.1 (5)	16.0 ± 4.2 (5)	17.4 ± 3.5 (5)
Apomorphine	0.5	14.0 ± 0.9 (7)	13.3 ± 1.0 (7)	16.0 ± 2.5 (7)	13.0 ± 4.1 (7)
SKF 38393	1.5	12.7 ± 2.7 (7)	13.0 ± 2.4 (7)	10.5 ± 2.8 (6)	10.3 ± 1.9 (6)
Bromo-LSD	5	1.5 ± 0.7 (5)	1.8 ± 0.6 (5)	2.2 ± 0.7 (6)	2.3 ± 0.9 (6)
Ergocriptine	5	16.8 ± 2.3 (5)	17.0 ± 2.7 (5)	17.9 ± 2.2 (9)	17.2 ± 2.7 (9)
Ergocornine	5	9.0 ± 1.3 (6)	10.2 ± 1.8 (6)	13.3 ± 1.6 (6)	13.2 ± 2.3 (6)
S3608	40	9.2 ± 1.7 (5)	7.4 ± 1.5 (5)	9.8 ± 1.2 (8)	8.7 ± 0.8 (9)

Means ± 1 S.E.M. are shown. The values in parentheses indicate the number of animals examined.
None of the differences between saline and AMPT, or between single and double lesions achieved statistical significance ($P > 0.05$).

Table 3. Drugs causing contraversive rotation in animals with a unilateral (single) or bilateral (double) 6-hydroxydopamine lesion of the medial forebrain bundle but which showed a reduction in rate of rotation following pretreatment with AMPT (200 mg/kg i.p. 1 hr previously)

Drug	Dose (mg/kg)	Circling (rotations/min)			
		Single lesion		Double lesion	
		Saline	AMPT	Saline	AMPT
CM 29-712	0.5	16.8 ± 5.2 (5)	6.6 ± 2.3* (5)	13.7 ± 2.5 (6)	4.2 ± 1.1* (6)
Bromocriptine	10	13.0 ± 0.7 (7)	7.9 ± 0.6* (7)	20.0 ± 2.5 (7)	9.9 ± 1.8* (7)
ET 495	40	10.6 ± 1.4 (5)	6.6 ± 1.2* (5)	9.2 ± 1.4 (9)	5.8 ± 1.5* (9)

Means ± 1 S.E.M. are shown. The values in parentheses indicate the number of animals examined.
* $P < 0.05$ (comparing saline to AMPT). None of the differences between single and double lesions achieved statistical significance ($P > 0.05$).

The effect of SKF-525A on rotation

Animals with a single 6OHDA lesion were pretreated with SKF-525A (75 mg/kg i.p.) 30 min prior to administration of some dopamine agonists in order to inhibit monooxygenase drug metabolising activity. The contraversive rotation induced by apomorphine (0.5 mg/kg s.c.) was unaffected by this procedure (Table 4). However, of those compounds showing AMPT sensitivity, SKF-525A inhibited the contraversive rotation induced by bromocriptine (5 mg/kg i.p.) and ET 495 (40 mg/kg i.p.), but not that provoked by CM 29-712 (0.5 mg/kg i.p.) (Table 4).

DISCUSSION

The results of this investigation confirm the known ability of the 6OHDA-lesioned rotating-rat model to distinguish between directly acting dopamine agonists, such as apomorphine, and indirectly acting drugs requiring intact dopamine pre-synaptic events [1]. This latter group includes compounds releasing dopamine, such as amphetamine, and other compounds, such as amantadine [14] and S1694 [15], whose precise mechanism of action remains unknown. The difference between the groups is emphasised by the opposing direction of rotation produced, the inability of indirectly acting compounds to produce rotation in the double-lesion model and the inhibitory effect of AMPT on the ipsiversive circling produced by indirect dopamine agonists.

However, other dopamine agonists, bromocriptine, ET 495 and CM 29-712, caused contraversive rotation in both models, and showed sensitivity to the effects of AMPT. These drugs were easily distinguished from the indirectly acting compounds by the production of contraversive rotation, the induction of active circling in the double-lesion model, and the only partial inhibition of circling caused by AMPT. But although they cause functional changes associated with direct activation of post-synaptic dopamine receptors, this action is sensitive to disruption of pre-synaptic events by AMPT.

AMPT has a number of actions, but it is primarily thought of as an inhibitor of tyrosine hydroxylase [16]. It is not easy to see why inhibition of synthesis of dopamine, or noradrenaline, or both should disrupt circling provoked by bromocriptine, CM 29-712 and ET 495. One possibility considered was that such circling depended on a combination of a direct post-synaptic action on the denervated receptors on the side of the 6OHDA nigrostriatal lesions, with a pre-synaptic action mediated via intact mesolimbic dopamine pathways to the nucleus accumbens provoking locomotion. It was for this reason that we studied the effect of these and all other dopamine agonists in the double 6OHDA-lesioned rodent model [9]. In the latter, ascending dopamine pathways to one striatum and mesolimbic system are destroyed on one side, and similar ascending pathways to the opposite mesolimbic areas are destroyed on the other side, leaving intact only one nigro-

Table 4. The effect of pretreatment with SKF-525A (75 mg/kg i.p. 30 min previously) on the rate of rotation in animals with a unilateral 6-hydroxydopamine lesion of the medial forebrain bundle induced by directly acting dopamine agonists which are sensitive to the effects of AMPT (200 mg/kg i.p. 1 hr previously) pretreatment

Drug	Dose (mg/kg)	Circling (rotations/min)	
		Saline	SKF-525A
Apomorphine	0.5	20.4 ± 6.2 (7)	19.8 ± 8.1 (7)
CM 29-712	0.5	21.3 ± 2.8 (7)	20.1 ± 5.3 (7)
Bromocriptine	10	14.8 ± 3.9 (7)	4.9 ± 2.2* (7)
ET 495	40	16.1 ± 2.2 (8)	9.6 ± 1.2* (8)

Means ± 1 S.E.M. are shown. The values in parentheses indicate the number of animals examined.
* $P < 0.05$ (comparing saline to SKF-525A).

striatal pathway. In such animals, all dopaminergic effects upon the locomotor-driving nucleus accumbens would have to be post-synaptic. However, bromocriptine, CM 29-712 and ET 495 were equally effective in causing contraversive circling (that is contraversive to the 6OHDA lesion destroying both nigral and mesolimbic dopamine pathways) in the double-lesioned as in the single-lesioned 6OHDA model, and the circling that they produced in the double 6OHDA-lesioned animals also was reduced by prior treatment with AMPT.

In the double 6OHDA-lesioned animals, the only remaining pre-synaptic site on which dopamine agonists could act would be on the side with the remaining intact nigrostriatal dopamine pathway [9], that is the side to which bromocriptine, CM 29-712 and ET 495 caused circling. It is difficult to see how inhibition of dopamine synthesis in those remaining nigrostriatal dopamine fibres should reduce circling; indeed, if anything, such an effect would have been expected to increase the rates of circling by increasing the degree of asymmetry of striatal dopamine stimulation. Another possible effect of AMPT might have been to induce a change in sensitivity of the post-synaptic dopamine receptor on the remaining intact side in double or single 6OHDA-lesioned animals. However, AMPT was administered only 1 hr before the dopamine agonists, and in that short time interval any change in the rate of synthesis of new catecholamines scarcely has time to alter post-synaptic receptor sensitivity. Bromocriptine and CM 29-712 certainly act on a number of other neuronal systems, including noradrenaline and 5HT [17–20], but this also applies to other compounds not sensitive to AMPT, for example the closely related derivative CF-25-397 [19, 21]. Bromocriptine at least acts as a partial agonist [22] but this also is true of apomorphine [23].

In searching for an explanation as to why AMPT should inhibit the effects of bromocriptine, CM 29-712 and ET 495, we were struck by the fact that for both bromocriptine and ET 495 some evidence has been obtained to suggest that active metabolites were involved in the dopamine agonist actions of both drugs. Thus, Silbergeld *et al.* [24] had suggested that the hypothermia induced in rats by bromocriptine was reversed by pretreatment with the monooxygenase inhibitor SKF-525A. Although Keller and Da Prada [25] had been unable to replicate this finding, and had also found that bromocriptine was capable of decreasing striatal homovanillic acid levels after SKF-525A, we [11] had shown that circling induced by bromocriptine also could be decreased by SKF-525A pretreatment. As far as ET 495 was concerned, earlier consideration had been given to the role of metabolites in its actions, because of its inability to alter dopamine-sensitive striatal adenylate cyclase [26]. In the present studies we confirmed that the circling induced by bromocriptine and ET 495 could be partially inhibited by prior treatment with SKF-525A, but that induced by apomorphine and CM 29-712 was unaffected by such a pretreatment. Why SKF-525A should inhibit the behavioural effects of bromocriptine and ET 495 is presently unknown, but the fact that the actions of CM 29-712 were unaffected, yet were susceptible to AMPT, suggested that the latter was not interfering with certain dopamine agonist actions by an effect upon active metabolites. It has been argued that the inhibitory effects of SKF-525A on bromocriptine-induced circling are due to sedation caused by this agent [27]. However, if this were true, it would be necessary to explain why rotation induced by apomorphine and CM 29-712 was unaffected.

We are unable to find any other convincing action of AMPT to explain its effects upon circling induced by bromocriptine, CM 29-712 and ET 495. AMPT is itself metabolised to active amines such as α-methyl-*p*-tyramine [28], but it is difficult to see why these should specifically affect the actions of these three drugs. We know of no data on the effect of AMPT on the penetration of different dopamine agonists into brain and clearly this must be investigated.

In the present study we have employed only a single dose of a large number of agonist compounds. Perhaps a clearer picture will emerge when subsequently we examine a range of doses of selected compounds from each agonist category. Additionally we could include studies of behavioural antagonism by a range of neuroleptics or indeed an extensive biochemical investigation, but it is difficult to see how such work in itself would aid clarification of the present findings.

Although at present we can provide no satisfactory answer for the observed phenomenon it is interesting that two of the three anomalous dopamine agonists, namely bromocriptine [29–32] and ET 495 [33], undoubtedly possess potent anti-Parkinsonian actions in man. Interestingly, CM 29-712 was mainly effective against Parkinsonian tremor (Sandoz Ltd, personal communication), an effect also prominent during treatment with ET 495. It must be important to find out why their effects in animals are sensitive to AMPT, if only to discard the notion that this indicated a reliance upon pre-synaptic dopamine mechanisms. This would not seem to predict a useful action in Parkinson's disease, in which dopamine neurones die, yet bromocriptine and ET 495 possess potent therapeutic actions in that illness.

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