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COMMUNICATIONS

Cholinergic modification of abnormal involuntary movements induced in the guinea-pig by intrastriatal dopamine

The modulation of motor function is considered to depend, at least in part, on an interaction between extrapyramidal dopaminergic and cholinergic mechanisms (Klawans, 1973). It is possible that dysfunction in such a transmitter balance may be a contributory factor to motor abnormalities and, in particular, the concept of a dopamine-acetylcholine balance has been applied to an understanding of the tardive dyskinesias which result from long term neuroleptic therapy (Gerlach, Reisby & Randrup, 1974). Drugs which block dopamine or enhance acetylcholine activity appear to alleviate the dyskinesias and, conversely, drugs which enhance dopamine or block acetylcholine mechanisms have been shown to exacerbate the dyskinesias (Gerlach & others, 1974; Marsden, Tarsy & Baldessarini, 1974).

However, the importance of these observations to the pathogenesis of abnormal involuntary movements has not been investigated in the laboratory since a suitable animal model has not been available. Therefore, the recent demonstration in our laboratories that intrastriatal dopamine or dopamine-like agents, can evoke abnormal involuntary movements was of great interest (Costall, Naylor & Pinder, 1974a, b). These involuntary movements particularly involved the oral region and superficially resembled certain components of tardive dyskinesias (Marsden, 1974). Initial tests on this model using drugs which interfere with dopaminergic mechanisms indicated a relevance to the clinical situation. Thus, the experimental dyskinesias were shown to be highly resistant to drug teatment similarly to the clinical dyskinesias which are also generally resistant to drug therapy with the exception of large doses of neuroleptic agents and tetrabenazine (Marsden, 1974). However, one neuroleptic having particular clinical efficacy is pimozide (Calne, personal communication; Fog & Pakkenberg, 1970) and this agent was shown to completely reverse the animal dyskinesias (Costall & Naylor, 1974).

The present studies were undertaken to further test the 'model' by determining whether drugs which alter acetylcholine function will modify the animal dyskinesias in the same manner as reported from the clinic, that acetylcholine agonists will reduce whilst acetylcholine blocking drugs enhance the severity of dyskinesias (Klawans, 1973; Gerlach & others, 1974).

The studies used male Dunkin-Hartley guinea-pigs weighing 400 to 500 g. Cannulae for intracerebral injections were stereotaxically implanted in the caudate-putamen under sodium pentobarbitone anaesthesia and using the techniques previously detailed (Costall & others, 1974b). Animals were used 2 to 3 weeks after the operation. Nialamide (75 mg kg^{-1}) was administered intraperitoneally (i.p.) 2 h before intrastriatal dopamine (100 μg, 1 μl) (see Costall & others, 1974b for details). Cholinomimetic agents [RS86, spiro-(*N'*-methyl-piperidyl-4')-*N*-ethyl succinimide hydrogen fumarate, Sandoz; physostigmine sulphate, BDH; pilocarpine nitrate, BDH] and cholinolytic agents (atropine sulphate, Sigma; dexbenzetimide, Janssen; orphenadrine hydrochloride, Brocades) were prepared in distilled water or a minimum quantity of ascorbic acid (dexbenzetimide) and administered in a volume of 1 ml kg^{-1} (i.p.). Doses were calculated as base. The behavioural observations of dyskinesias were carried out in a sound-proofed, diffusely illuminated room maintained at a

temperature of 21 ± 1°. The dyskinesias were characterized as indicated in Table 1 and detailed by Costall & others (1974b).

The abnormal involuntary movements induced in the guinea-pig by intrastriatal dopamine characteristically involved the oro-facial and neck regions. Hyperactivity also developed. These effects have been shown to be specific for dopamine whereas whole body rocking or head and neck jerks also occur after intrastriatal solvent and are considered to be injection artifacts (Costall & others, 1974b). The dyskinesias developed within 60 to 90 min of the dopamine injection and persisted for at least 6 h.

Table 1. *Dyskinesias induced by dopamine in the guinea-pig and their modification by cholinergic/cholinolytic drugs.*

			Dyskinesias				
Peripheral treatment	Dose mg kg^{-1} i.p.	Intra-striatal dopamine μg μl^{-1}	Gnawing, biting, licking	Severe head and neck twisting	Hyper-activity	Whole body rocking	Head and neck rocking
Solvent	—	Solvent	0/8	0/8	0/8	1/8	2/8
		6·25	5/8(P)	0/8	0/8	1/8	2/8
		12·5	7/8(P)	0/8	0/8	1/8	1/8
		25	8/8(P)	0/8	2/8	0/8	1/8
		50	7/8	1/8	8/8	0/8	3/8
		100	8/8	3/8	8/8	2/8	4/8
Eserine	0·5	100	7/8	4/8	7/8	2/8	3/8
	1·0	100	3/8	2/8	1/8	0/8	3/8
	2·0*	100	0/8	0/8	0/8	0/8	5/8
RS86	0·5	100	6/8	2/8	6/8	2/8	1/8
	1·0	100	6/8	1/8	5/8	1/8	3/8
	2·0	100	0/8	0/8	0/8	0/8	6/8
	4·0	100	0/8	0/8	0/8	0/8	7/8
Pilocarpine	0·25	100	6/8	0/8	3/8	2/8	3/8
	0·5	100	2/8	1/8	7/8	1/8	5/8
	1·0	100	0/8	0/8	3/8	0/8	5/8
	2·0	100	0/8	0/8	0/8	1/8	6/8
	4·0	100	0/8	0/8	0/8	2/8	7/8
Atropine	0·25	25	6/8(P)	0/8	7/8	1/8	2/8
	2·5	25	7/8(P)	0/8	7/8	0/8	2/8
	25·0	25	6/8(P)	1/8	6/8	3/8	4/8
Dexbenzetimide	0·1	25	8/8(P)	0/8	4/8	0/8	3/8
	0·5	25	6/8(P)	0/8	6/8	2/8	4/8
	1·0	25	6/8(P)	0/8	5/8	3/8	6/8
	5·0	25	6/8(P)	0/8	6/8	2/8	6/8
Orphenadrine	3·13	25	7/8(P)	0/8	3/8	0/8	2/8
	6·25	25	6/8(P)	0/8	5/8	1/8	5/8
	12·5	25	6/8(P)	1/8	7/8	0/8	6/8
	25·0	25	8/8(P)	0/8	6/8	1/8	7/8
Atropine + eserine	2·5 1·0	100	7/8	1/8	6/8	1/8	1/8
Orphenadrine + pilocarpine	12·5 1·0	100	8/8	0/8	6/8	1/8	0/8
Dexbenzetimide + RS86	1·0 2·0	100	8/8	1/8	5/8	0/8	3/8

*Animals died within 60 min of injection.

The dyskinesias were simply assessed as present or absent with the exception of the gnawing/biting which could be differentiated into a periodic or continuous behaviour.

The administration of cholinomimetic agents (RS 86, pilocarpine, eserine) rapidly (2 to 15 min) caused complete abolition of all features of the dopamine effect (established at maximum intensity) with the exception of some small head and neck movements (Table 1). However, the time course for inhibition of hyperactivity was noticeably shorter (by 35 to 50 min for larger doses of pilocarpine) than that for the inhibition of the dyskinesias (total 15 to 40 min, lower doses, 60 to 120+ min, higher doses). The animals simultaneously developed signs of peripheral cholinergic stimulation—lachrymation, salivation, defaecation—and muscle fasciculations (eserine).

The dyskinesias induced by a 'threshold' dose of dopamine (25 μg, 1 μl) were periodic and were not intensified by pretreatment with dexbenzetimide (2h) or a subsequent administration of atropine or orphenadrine. However, the effects of RS86, pilocarpine or eserine were prevented by pretreatment with dexbenzetimide (2h), orphenadrine or atropine (30 min) (Table 1).

Thus, the animal 'model' of abnormal involuntary movements has been shown to respond to cholinergic and neuroleptic therapy in a similar manner to the clinical condition. It is, therefore, suggested that the ability of dopamine to induce abnormal movements from the striatum of the guinea-pig may have some relevance to an investigation of the pathophysiology of dyskinesias. The mechanisms for dyskinesia induction appear to involve both acetylcholine and dopamine but the relation between these two systems is not clear since atropine, orphenadrine and dexbenzetimide failed to enhance the dopamine dyskinesias. This would indicate that the acetylcholine system normally plays a subservient role to dopamine. The precise effect of an anti-acetylcholine agent on the dyskinesias in the clinic would, therefore, depend on the functional activity of the acetylcholine system which may vary with the degree of pathophysiological disruption to striatal mechanisms. This may help to explain the equivocal clinical results where antiacetylcholine agents have been found to either exacerbate or be ineffective against tardive dyskinesias (Klawans, 1973; Gerlach, & others, 1974). The present studies thus support the concept of an acetylcholine system moderating a dopamine dysfunction in dyskinesias. Further studies are required to elucidate the precise site of this interaction.

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REFERENCES

COSTALL, B. & NAYLOR, R. J. (1974). *Eur. J. Pharmac.*, in the press.

COSTALL, B., NAYLOR, R. J. & PINDER, R. M. (1974a). *J. Pharm. Pharmac.*, **26**, 753–762.

COSTALL, B., NAYLOR, R. J. & PINDER, R. M. (1974b). *Eur. J. Pharmac.*, in the press.

FOG, R. & PAKKENBERG, H. (1970). *Acta neurol. scand.*, **46**, 249–251.

GERLACH, J., REISBY, N. & RANDRUP, A. (1974). *Psychopharmacologia (Berl.)*, **34**, 21–35.

KLAWANS, H. L. (1973). *The Pharmacology of Extrapyramidal Movement Disorders.* Monographs in Neural Sciences, Vol. 2. Basel: Karger.

MARSDEN, C. D. (1974). *The Neuropharmacology of Abnormal Involuntary Movement Disorders* (The Dyskinesias). *Modern Trends in Neurology.* Vol. 6. London: Butterworth.

MARSDEN, C. D., TARSY, D. & BALDESSARINI, R. J. (1974). Seminars in Psychiatry, in the press.