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COMMUNICATIONS

Long-lasting anti-tremor activity induced by 2-Br-α-ergocryptine in monkeys

It has recently been demonstrated that L-dopa and a dopamine receptor stimulating agent, 1-(2″-pyrimidyl)-4-piperonyl-piperazine (ET 495) (Corrodi, Fuxe & others, 1971; Corrodi Farnebo & others, 1972), can relieve surgically induced tremor in monkeys and concomitantly evoke involuntary movements (Goldstein, Battista & others, 1973). Recently, ergotoxine alkaloids, such as ergocornine and 2-Br-α-ergocryptine (CB 154), have been shown to be dopamine receptor stimulating agents (Hökfelt & Fuxe, 1972; Corrodi, Fuxe & others, 1973; Fuxe, 1973). The results presented in this paper show that repeated administration of CB 154 results in long-lasting relief from tremor in monkeys with ventromedial tegmental lesions.

Five green monkeys (*Cercopithecus sabaeus*) were used, and unilateral radiofrequency lesions were induced in the ventromedial tegmental region of the brain stem (Poirier & Sourkes, 1965; Goldstein, Anagnoste & others, 1969; Battista, Fuxe & others, 1974). Hypokinesia of the contralateral extremities appeared immediately afterward. In three monkeys (Nos. I–III) a resting tremor of 4 to 6 Hz developed five to seven days later. One monkey (No. IV) developed only a rare spontaneous resting tremor and another monkey (No. V) developed tremor only after administration of harmaline (Poirier, Sourkes & others, 1966).

Injections with CB 154-mesiliate did not begin until one month after the lesion. All doses refer to the base. Recordings of tremor were made by means of a transducer attached to the extremities and were recorded on an electroencephalograph. The involuntary movements (IM) were observed visually and could be divided into two types (see Sassin, Taub & Weitzman, 1972; Goldstein, Anagnoste & others, 1973). IM of type I (see Table 1) are mainly related to changes in emotional behaviour (restlessness, aggressiveness) whereas IM of type II mainly can be described as hyperkinesias (chorea-like movements, various types of stereotyped movements, etc.).

The results are summarized in Table 1.

The administration of CB 154 (6 mg kg^{-1}, i.p.) resulted in the disappearance of the tremor for 1–27 h. In monkey No. IV the single administration of CB 154 resulted in the development of involuntary movements of Types I and II for a period of 24 h. Repeated administration of CB 154 (5–8 mg kg^{-1}, i.p.) resulted in the disappearance of the tremor for at least 48 h. After cessation of treatment the intensity of the tremor was diminished for another 24–48 h. The long-lasting anti-tremor effect of the drug was further illustrated when CB 154 treatment was interrupted on the third day in monkey No. I (Table 1). At this time (day 7) the administration of CB 154 resulted in a much longer lasting disappearance of the tremor (approx. 10 h) as compared with the single administration of the drug on the first day of treatment (approx. 1 h). The repeated administration of CB 154 resulted also in the development of involuntary movements of types I and II (see Table 1). However, the involuntary movements were of moderate intensity and of shorter duration than the drug induced relief of the tremor. Furthermore, only one of the monkeys with spontaneous tremor (ST) developed unilateral chorea-like movements. Marked IM of types I and II were only observed in monkey No. V which lacked ST and only developed tremor after harmaline treatment. Compulsive circling behaviour

Table 1. *The effect of single and repeated injections of CB 154 on spontaneous tremor (ST) and on development of involuntary movement (IM) in monkeys with ventromedial tegmental lesions.*

Monkey	Treatment	Day	Dose (i.p.) mg kg^{-1}	Antitremor activity Latency (h)	Duration (h) Blockade	Reduction	Involuntary movements Type I (h)	Type II (h)	Remarks
	Single injections								
No. I (ST)	CB 154		6	1	1	none	none	none	Sedation hypersalivation
	Repeated injections								
No. I	CB 154	1	5		none	0·3	none	none	
	CB 154	1, 4 h	5		none	1	slight	none	
No. I	CB 154	2	8		0·25	25	moderate >25	moderate >25	Restlessness (I) chewing (II) tongue-rolling (II) grooming (II)
No. I	CB 154	3	8		48	48	moderate 30	moderate 30	Hypokinesia also disappeared; IM same as day 2
No. I	CB 154	7	6		10	>14	moderate >24	moderate >24	IM same as day 2
No. I	CB 154	8	4		<24	24	moderate <24	moderate <24	IM same as day 2 except chorea-like movements for 7 h
No. II (ST)	CB 154	1	3						
No. II	CB 154	2	6	0·6	>23		slight 7	none	Sedation for 1 h immediately after injection
No. II	CB 154	3	6		<48	24	moderate >7 <20	moderate >7 <20	Restlessness (I) grooming (II)
No. III (ST)	CB 154	1	6 i.m.	0·8	none	3	none	none	
No. III	CB 154	2	6 i.m.	0·25	0·25	>24	moderate >7 <22	none	Restlessness (I) (I) Chattering (I)
No. III	CB 154	3	6 i.m.	none	>48	48	moderate <24	none	IM as on day 2 plus aggressiveness
No. IV (rare ST)	CB 154		6 i.m.	0·75	27		slight 24	slight 24	Hypokinesia reduced chattering (I) restlessness (I) licking (II)
No. V (No. ST)	CB 154		2 i.m.	0·5			marked 22	marked 22	Initial sedation (0·5 h) restlessness irritability (I) hypersensitivity (I) aggressiveness (I) unilateral chorea-like movements (II)
No. V	CB 154		8 i.m.	0·5			marked >27 <48	marked >27 <48	IM same as after 2 mg kg^{-1}, hypokinesia reduced

towards the denervated side was observed in monkeys Nos. I and II after CB 154. The hypokinesia was reduced by CB 154 in 3 monkeys out of 5 (Nos. I, IV and V).

Dopa and a dopamine receptor stimulating agent, ET 495 (Corrodi & others, 1971, 1972) have previously been shown to counteract tremor and in somewhat higher doses to cause involuntary movements in monkeys with ventromedial tegmental lesions (Goldstein & others, 1973). These results have led to the hypothesis that these phenomena are controlled by dopamine receptors in the forebrain and that exaggerated activity of the dopamine receptor will cause appearance of IM. The present findings give further support for this hypothesis. The data also suggest that CB 154 could be a powerful anti-tremor drug in parkinsonian patients with unusually long-lasting actions. In this respect it has considerable advantages over dopa and ET 495, although the latter compound also possesses relatively long-lasting actions. Furthermore, the IM are only of moderate intensity after CB 154 and have not been seen for more than a day, whereas the anti-tremor activity can last for 4–5 days. Chorea-like movements were only observed in one of the three monkeys with ST. It is of interest that the most severe IM were observed in the monkey that exhibited tremor only after

harmaline treatment. Since IM of type II are believed to result from marked activation of supersensitive dopamine receptors, which have developed their change in sensitivity as a result of the degeneration of the ascending dopamine pathways (see book edited by de Ajuriaguerra and Gauthier) it seems as if development of tremor also required damage to other pathways besides the dopamine pathways (see Poirier, Bouvier & others, 1969). Otherwise, tremor should have developed independently of harmaline treatment in view of the existence of a degeneration of the dopamine pathway as suggested by the demonstrated signs of receptor supersensitivity (see above).

It should be mentioned also that hypokinesia was reduced in 3 of the 5 monkeys tested, suggesting that this symptom is also controlled to some extent by dopamine receptors.

In conclusion, the dopamine receptor stimulating agent CB 154, belonging to the ergotoxine alkaloids, causes a prolonged blockade of tremor in monkeys with ventromedial tegmental lesions which is partly associated with development of involuntary movements and reduction of hypokinesia.

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Departments of Neurosurgery and Psychiatry, New York University Medical Center, New York, N.Y. U.S.A.

T. MIYAMOTO
A. BATTISTA
M. GOLDSTEIN

Department of Histology, Karolinska Institutet, S 104 01 Stockholm, Sweden.

K. FUXE

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