JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 1998, 49, 2, 311—317

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MUSCLE RIGIDITY INDUCED BY FLUPHENAZINE IN RATS IS ANTAGONIZED BY L-DOPA, AN ANTIPARKINSONIAN DRUG

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The aim of the present study was to find out whether the clasic neuroleptic fluphenazine is a good model compound for inducing parkinsonian-like muscle rigidity in rats. The muscle tone was measured as resistance developed by the rat's hind foot to passive flexion and extension. Fluphenazine in doses of 0.4—3.0 mg/kg ip induced a dose-dependent increase in the hind foot resistance to passive movements. The muscle rigidity induced by fluphenazine (1.5 mg/kg ip) was counteracted in a dose-dependent manner by the main antiparkinsonian drug L-DOPA (25-75 mg/kg ip). The present results suggest that the fluphenazine-induced muscle rigidity may be a useful model of parkinsonian rigidity.

Key words: *parkinsonism, muscle rigidity, fluphenazine, L-DOPA.*

INTRODUCTION

It is commonly accepted that degeneration of dopaminergic nigrostriatal neurons is the main cause of Parkinson's disease (1, 2). It has been postulated that the loss od dopamine in the striatum (80—98%) underlies such parkinsonian symptoms as muscle rigidity, akinesia (bradykinesia) and resting tremor (3, 4). This concept has allowed introduction of a substitutive therapy of this disease with L-DOPA (3, 4-dihydroxyphenalalanine), a dopamine precursor which easily penetrates the blood/brain barrier and is converted to dopamine in the brain (5). Despite the fact that L-DOPA induces many serious side-effects (psychoses, dyskinesias), it is still a basic drug in the treatment of Parkinson's disease (6).

The parkinsonian symptoms: akinesia, muscle rigidity and tremor, also occur as side-effects of antipsychotic therapy with typical neuroleptics in schizophrenia (2). It has been suggested that the neuroleptic-induced parkinsonism is due to a blockade of dopamine D2 receptors in the striatum (2). It is well known that typical neuroleptics induce catalepsy in laboratory

animals. This phenomenon is generally accepted as a model of drug-induced parkinsonism (cf. 7), which, however, seems to reflect parkinsonian akinesia rather than other parkinsonian symptoms (cf. 7). It has also been reported that the typical neuroleptic — haloperidol induces muscle rigidity in rats, measured as a tonic electromyographic (EMG) activity at rest (8), or increased muscle resistance to passive movements (9, 10). The latter effect in rats seems to represent well features of parkinsonian rigidity, because the increased muscle resistance was also observed in dopamine-depleted rats after reserpine and in animals whose the dopaminergic nigrostriatal pathway was lesioned with 6-hydroxydopamine (11, 12).

It has been shown that catalepsy induced by neuroleptics is inhibited by dopaminomimetics including L-DOPA (13, 14), however, data on a similar effect of L-DOPA on muscle rigidity are lacking.

The aim of the present study was to find out whether another typical neuroleptic, fluphenazine — which is known to produce strong parkinsonian symptoms in humans (15), induces muscle rigidity in rats, and to determine whether L-DOPA, the main antiparkinsonian drug, counteracts fluphenazine-induced muscle rigidity. To this end, like in the above-mentioned studies, we measured muscle tension, as resistance of the hind foot to passive flexion and extension.

MATERIALS AND METHODS

The experiment was carried out on female Wistar rats weighing approximately 250 g. Experimental groups consisted of 5—14 animals each.

Fluphenazine (Sigma) was dissolved in a 0.9% saline and was administered ip in four doses of 0.4, 0.75, 1.5 or 3 mg in a volume of 2 ml per kg of body weight. Madopar (Roche; 50 mg of L-DOPA + 12.5 mg of benserazide) was suspended in 2 ml of a saline solution containing a 5% polyethoxylated castor oil (Cremophor). Suspensions were freshly prepared prior to each injection. Madopar was administered ip in a volume to achieve doses of 25, 50 and 75 mg/kg of L-DOPA at 15 min after pretreatment with fluphenazine (1.5 mg/kg ip). Control animals received fluphenazine and the corresponding volume of vehicle instead of Madopar. All the animals were used only once.

Mechanographic measurements

Measurements started 30 min after administration of fluphenazine. Fifteen min before the start of measurements, each rat was placed for habituation in a metaplex cage which limited its movements. Its right, hind foot, which protruded from the opening at the bottom of the cage, was fastened to a metaplex block with an adhesive tape. The block was connected to a force sensor which recorded the resistance of the foot to passive movements (MMG, mechanical moment, torque) (modification of the previously described MMG method, (9, 16). The experiment involved successive passive movements (extension and flexion) of the rat's foot at the ankle joint by 25° with a velocity of 100°/s. One movement (extension or flexion) lasted 250 ms, and an interval between the successive movements was 30 s. The axis allowing rotations of the block was placed under the ankle joint. A down-movement started from the horizontal position. A successive up-movement

made the foot reassume the horizontal position. Movements of the block were executed with an electric engine under a PC control. An analogue-to-digital converter was used, and samples of the foot resistance were stored with a sampling frequency of 10 kHz. The difference between the maximum resistance and the value of the steady-state pressure of the foot on the force sensor before a movement was accepted as a value of the muscle tone.

Statistics

Experimental data were statistically analysed by the Kruskal-Wallis and the Wilcoxon-Mann--Whitney-U tests.

RESULTS

Fluphenazine administered ip in doses of 0.4—3.0 mg/kg increased dose-dependently muscle resistance of the rat's hind foot to passive extension and flexion, measured between 1 and 2 h after the injection (*Fig. 1*).

L-DOPA in doses of 25—75 mg/kg ip, injected 15 min after fluphenazine (1.5 mg/kg ip), antagonized dose-dependently muscle rigidity induced by that neuroleptic (*Fig. 2*). The effect of L-DOPA could already be seen during the first 10 min after injection and, after the highest dose lasted till the end of the experimental session (105 min after L-DOPA, 2 h after fluphenazine). Lower doses of L-DOPA lost their efficacy much earlier.

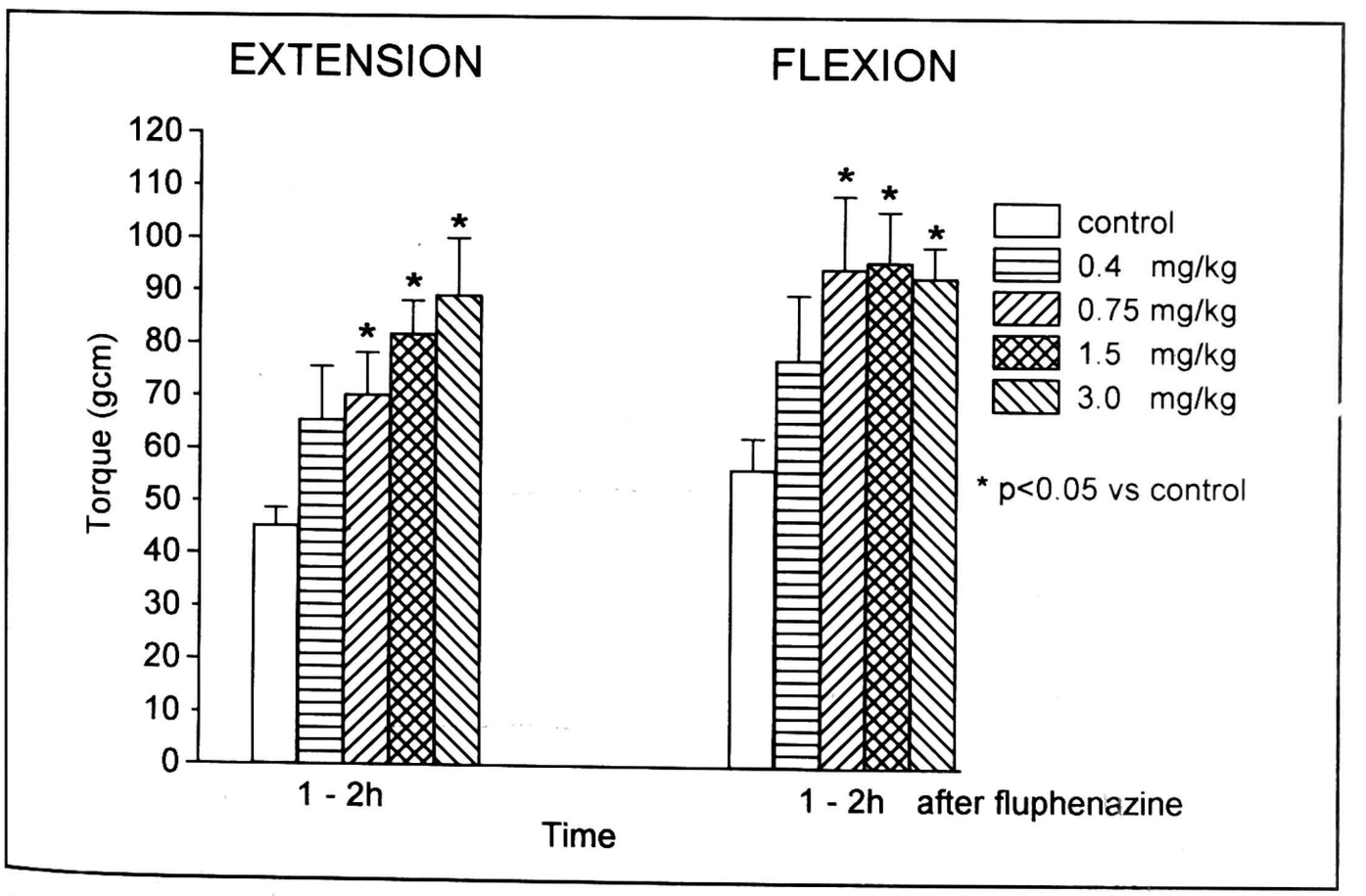

Fig. 1. The fluphenazine (0.4—3.0 mg/kg ip)-increased resistance of the rat's hind food, developed during passive extension and flexion of the foot in the ankle joint. Fluphenazine was injected 1 h before the start of measurements. Abscissa — time in hours after fluphenazine injection, ordinate — maximal resistance (in gcm = g × cm) of the hind foot).

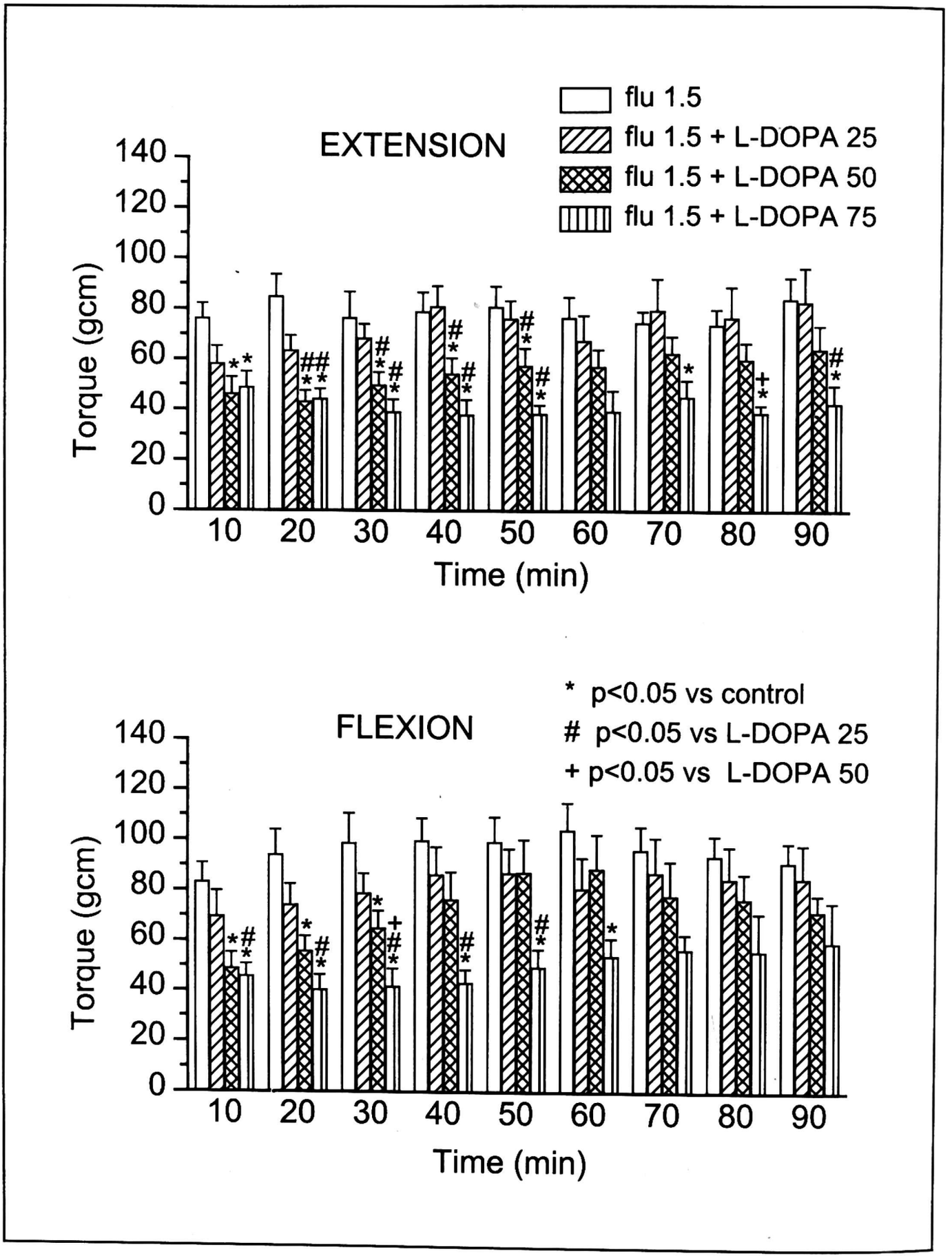

Fig. 2. The effect of Madopar (L-DOPA + benserazide, in mg of L-DOPA) on the fluphenazine (flu 1.5 mg/kg ip)-increased resistance of the rat' hind foot, developed during passive extension and flexion of the foot in the ankle joint. Fluphenazine was injected 30 min before, and Madopar — 15 min before the start of measurements. Abscissa — time in min, ordinate — maximal resistance (in gcm) of the hind foot.

DISCUSSION

The present study shows that fluphenazine injected to rats induces muscle rigidity, measured as an increase in muscle resistance developed in response to passive flexion and extension of the hind foot. In this respect the fluphenazine-induced effect is similar to that observed by us after another neuroleptic, haloperidol (10). Moreover, monoamine depletion induced by reserpine, or the bilateral lesion of 89% of dopaminergic nigrostriatal neurons due to 6-hydroxydopamine intranigral injection resulted in a similar increase in muscle resistance measured by the same method (11, 12). Furthermore, the present study indicates that the fluphenazine-induced muscle rigidity is antagonized by the commonly used antiparkinsonian drug L-DOPA. All these data suggest that the fluphenazine-induced muscle rigidity reflects rigidity seen in the course of Parkinson's disease or after treatment with high doses of classic neuroleptics. This conclusion is supported by the finding that fluphenazine also evokes catalepsy, another parkinsonian symptom (13, 17).

As a rule, the catalepsy induced by fluphenazine is measured not earlier than 2 h after injection. A few hours are needed to obtain a high level of the catalepsy score (13, 17). When the catalepsy is measured 2—5 h after fluphenazine injection, high doses of L-DOPA (100—200 mg/kg) are necessary to inhibit this phenomenon. Furthermore, the antagonizing effect of L-DOPA seems fairly weak (13). Therefore, in order to examine the antagonistic effect of low doses of this antiparkinsonian drug, in the present study we started our measurements of the muscle tension much earlier, i.e. already at 30 min after a high dose of fluphenazine, L-DOPA being injected 15 min later. As expected, the muscle rigidity induced by fluphenazine was dose-dependently antagonized by much lower doses of L-DOPA than those necessary to antagonize the fluphenazine-induced catalepsy (13, 17).

Typical neuroleptics such as haloperidol and fluphenazine are potent antagonists of dopamine D2 receptors (18). It has been postulated that both the catalepsy and muscle rigidity induced by these drugs result from blockade of dopamine D2 receptors in the corpus striatum (8, 19). The affinity of these drugs for striatal dopamine D2 receptors is at least two orders of magnitude higher than the affinity of dopamine (20, 21). Therefore it is not surprising that only high doses of L-DOPA, which is converted to dopamine, are able to antagonize catalepsy measured at the peak of the fluphenazine action (13). Since in the present study muscle rigidity was measured at a relatively short time after fluphenazine injection, blockade of dopamine D2 receptors probably did not fully develop, hence lower doses of L-DOPA were sufficient to antagonize that effect in a dose-dependent manner. However, irrespective of the

above methodological and pharmacokinetic differences both the fluphenazine-induced catalepsy and muscle rigidity seem to be valuable tools for screening new potential antiparkinsonian drugs.

Acknowledgements: The paper was supported by a statutory found of the Institute of Pharmacology, Polish Academy of Sciences, and partly by Deutsche Forschungsgemeinschaft [Grant DFG 436 Pol 113/63/0(S)] and Bundesministerium für Bildung und Forschung (BMBF), Projektträger: DLR Internationales Büro (Project X084.61)] which enabled the authors to purchase necessary equipment and to cover their travelling expenses and subsistence in Berlin.

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R e c e i v e d: February 12, 1998.
A c c e p t e d: April 15, 1998

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