Naunyn-Schmiedeberg's Arch. Pharmacol. 300, 195–198 (1977)

Naunyn-Schmiedeberg's
Archives of
Pharmacology

Short Communication

Lisuride*, a Potent Drug in the Treatment of Muscular Rigidity in Rats

D. LOOS, K. HALBHÜBNER, and H. HERKEN

Pharmakologisches Institut der Freien Universität Berlin, Thielallee 69/73, D-1000 Berlin 33

Summary. Persistent and transient muscular rigidities were induced by 6-aminonicotinamide (6-AN) and reserpine, respectively, in rats and recorded electromyographically.

Very low doses of lisuride (25 or 50 µg/kg) reduced or abolished the increased electromyographic activity in the gastrocnemius muscle. Similar results were obtained with the combination of L-DOPA (100 mg/kg) plus benserazide (25 mg/kg). Methysergide was inactive. It is suggested that lisuride could be of value in the therapy of Parkinson's disease.

Key words: 6-Aminonicotinamide – Reserpine – L-DOPA – Lisuride – Muscular rigidity.

INTRODUCTION

The administration of 6-aminonicotinamide (6-AN) to rats (10 mg/kg i.p.) produces characteristic neurotoxic symptoms (Johnson and McColl, 1955; Sternberg and Philips, 1958; Wolf and Cowen, 1959; Coper and Herken, 1963) including a strong muscular rigidity of the hind limbs. Concomitant with the onset of the morphological lesions and metabolic changes which are first found in the neuroglial cells, especially in the spinal cord (Herken et al., 1973), spontaneous electrical activity increases in the gastrocnemius muscle (Herken et al., 1976; Halbhübner et al., 1977). The muscular rigidity of the hind limbs as well as the pathological activity in the electromyogram of the gastrocnemius muscle are irreversible.

Send offprint requests to H. Herken at the above address

* N-(D-6-methyl-8-isoergolenyl)-N',N'-diethylcarbamide hydrogen maleate

The neurotoxic syndrome produced by 6-AN may result from lesions in the extrapyramidal motor system in addition to those in the spinal cord, as Schneider (1971) found microscopic lesions in the red nucleus, the vestibular nuclei, and the reticular formation. It was, therefore, of interest, to compare the modification by drugs of the 6-AN-induced syndrome and of the reserpine-induced muscular rigidity.

Reserpine, administered to rats in high doses, is known to cause reproducible Parkinson-like symptoms with increased electromyographic activity which, in contrast to the changes induced by 6-AN, last only a few hours (Steg, 1964; Jurna and Lanzer, 1969; Morrison and Webster, 1973). Reserpine-induced rigidity has been proposed to result from an increased α-motoneurone activity and a decreased γ-motoneurone activity (Roos and Steg, 1964) due to an impaired balance of dopaminergic and cholinergic mechanisms in the brain (Barbeau, 1962). Both dopaminergic and cholinolytic substances have been shown to abolish reserpine-induced rigidity (Jurna and Lanzer, 1969; Jurna, 1976), and this effect was correlated with their clinical potency in the treatment of Parkinson's disease (Goldstein et al., 1975).

METHODS

The electromyograms were recorded from the gastrocnemius muscle of male Wistar rats (Hagemann, Extertal) by concentric needle electrodes. For quantitative analysis the signals were rectified and integrated by an analog computer (EAI 380 Analog Hybrid Computing System), and in each case the voltage was measured over a period of 20 s. The animals were given either 6-AN (10 mg/kg i.p.) several months before or reserpine (10 mg/kg i.v.) 1 h before the investigation. All drugs used were dissolved either in 0.9% saline or in 2% methylcellulose (L-DOPA). L-DOPA (100 mg/kg 30 min after pretreatment with 25 mg/kg of benserazide), lisuride (25 or 50 µg/kg), and methysergide (1 mg/kg) were administered i.p.

6-Aminonicotinamide was purchased from Roth (Karlsruhe) and L-dihydroxyphenylalanine from Serva (Heidelberg). Benser-

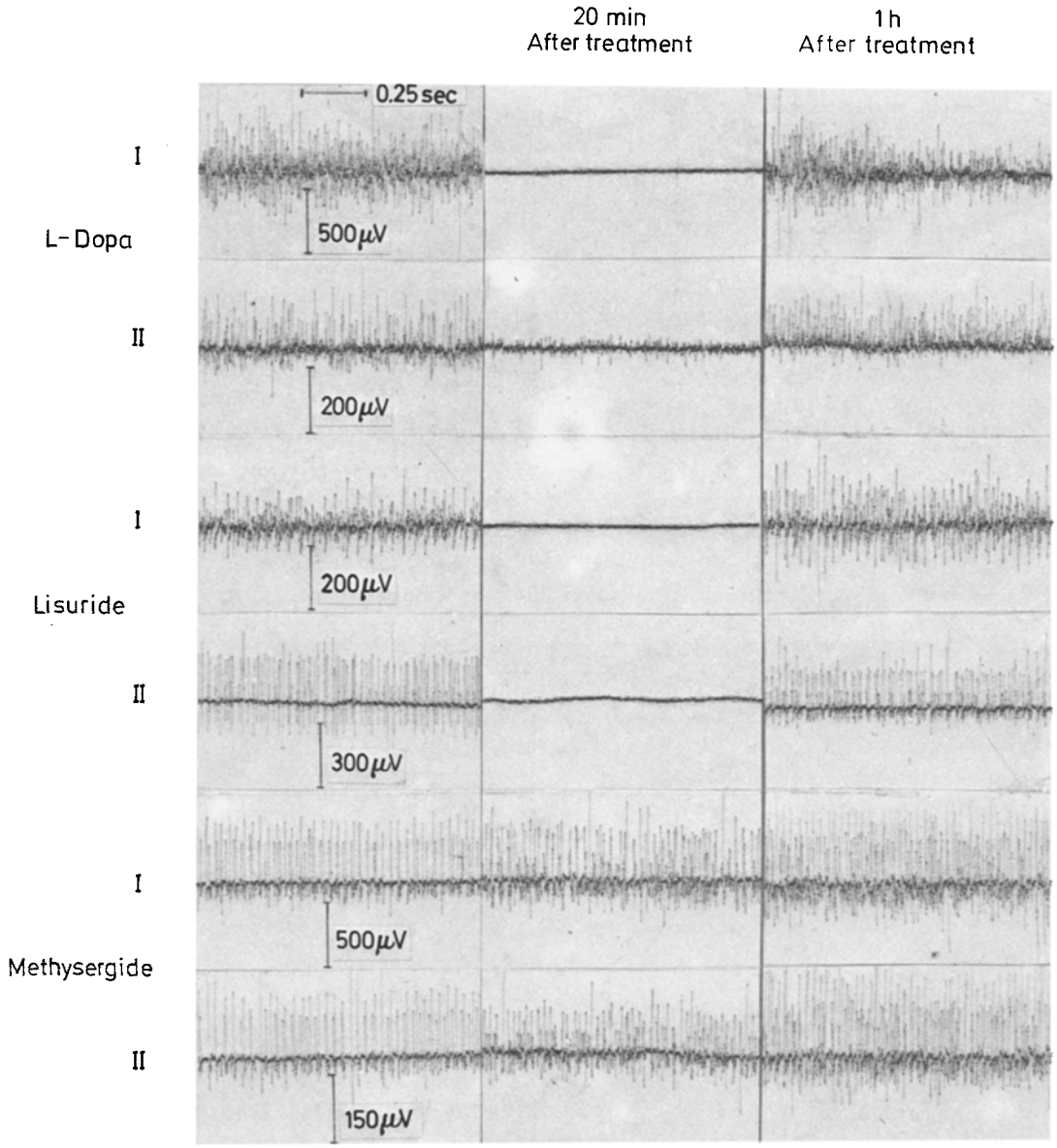

Fig. 1. Effects of L-DOPA (100 mg/kg) plus benserazide (25 mg/kg), lisuride (50 µg/kg) and methysergide (1 mg/kg) on the electromyographic hyperactivity recorded from the gastrocnemius muscle of 6 different rats pretreated with either 6-AN (I) (10 mg/kg) or reserpine (II) (10 mg/kg)

azide (Ro 4-4602) was a gift of Hoffmann-La Roche AG (Grenzach), lisuride of Schering AG (Berlin), methysergide of Sandoz AG (Basel), and reserpine (Serpasil) of Ciba-Geigy GmbH (Wehr).

RESULTS AND DISCUSSION

The similarity of muscular rigidity in the hind limbs of rats occurring after either reserpine or 6-AN led us to compare the effects of L-DOPA in these two models. Birkmayer and Hornykiewicz (1961) were the first to report on the successful treatment of Parkinson's disease with L-DOPA. These results were confirmed by many authors (Rinne and Sonninen, 1968; Barbeau, 1969; Calne and Sandler, 1970; Calne, 1973). L-DOPA has an indirect stimulating effect on the central nervous dopamine receptors by increasing the previously reduced dopamine levels both in patients suffering from Parkinson's disease (Davidson et al., 1971) and in reserpine-treated animals (Bertler, 1961; see Hornykiewicz, 1972).

The combination of L-DOPA with benserazide (Ro 4-4602) increases the central supply of L-DOPA by an inhibition of the peripheral aromatic amino acid decarboxylase (Pletscher and Bartholini, 1971). As shown in Figure 1, L-DOPA (100 mg/kg i.p.) 30 min after benserazide (25 mg/kg i.p.) abolished the sponta-

neous electromyographic activity induced by reserpine ($n = 8$) as well as by 6-AN ($n = 8$). This effect in rats pretreated with reserpine is in good agreement with the observations of other authors (Roos and Steg, 1964; Jurna and Lanzer, 1969).

In addition to the effect of L-DOPA we investigated the influence of lisuride on the electromyogram pattern in both models. Lisuride proved to possess a strong peripheral antiserotonergic (Votáva and Lamplová, 1961) and dopaminergic action in the central nervous system (Horowski and Wachtel, 1976; Kehr, 1977). Lisuride was very potent in reducing the electrical activity in both reserpine- and 6-AN-induced rigidity. A dose of 25 µg/kg of lisuride reduced the initial activity (100%) recorded from rats pretreated with 6-AN to 49.4% ± 18.4 SD and to 2.4% ± 3.4 SD in animals pretreated with reserpine. 50 µg abolished the spontaneous discharge in both cases as shown in Figure 1.

The lack of a depressant effect of the serotonin antagonist methysergide (1 mg/kg i.p.), another lysergic acid derivative, on the electromyogram ($n = 6$) in both cases excludes the possibility that the effect of lisuride was due to its antiserotonergic action (see Fig. 1).

The above results are in favour of the hypothesis that the persistent activity in the electromyogram of rats pretreated with 6-AN results from an increased α-motor activity as does reserpine rigidity, although an additional γ-hyperactivity cannot be excluded. This also applies for the pathophysiology of the extrapyramidal symptoms of Parkinson's disease. It is not yet clear, whether rigidity in Parkinson's disease is caused by a dysfunction of α- or γ-motor system (Calne, 1970; Wiesendanger, 1972).

The effect of lisuride in the reserpine model for screening anti-Parkinsonian agents (Goldstein et al., 1975; Jurna, 1976) and the similar effect found on the persistent muscular rigidity induced by 6-AN suggest that this drug could have potential usefulness in the therapy of Parkinson's disease.

Acknowledgement. The authors wish to thank Miss M. Kipsch for her skilful technical assistance.

REFERENCES

Barbeau, A.: The pathogenesis of Parkinson's disease: A new hypothesis. Can. med. Ass. J. **87**, 802–807 (1962)

Barbeau, A.: L-DOPA therapy in Parkinson's disease. A critical view of nine year's experience. Can. med. Ass. J. **101**, 791–800 (1969)

Bertler, Å.: Effect of reserpine on the storage of catecholamines in brain and other tissues. Acta Physiol. Scand. **51**, 75–83 (1961)

Birkmayer, W., Hornykiewicz, O.: Der L-3,4-Dioxyphenalanin-(=DOPA)-Effekt bei der Parkinson Akinese. Wien. Klin. Wochenschr. **45**, 787–788 (1961)

Calne, D. B.: Parkinsonism: Physiology, pharmacology and treatment. London: E. Arnold 1970

Calne, D. B. (Ed.): Progress in the treatment of Parkinsonism. Advances in Neurology, Vol. 3. New York: Raven Press 1973

Calne, D. B., Sandler, M.: L-DOPA and Parkinsonism. Nature **226**, 21–24 (1970)

Coper, H., Herken, H.: Schädigung des Zentralnervensystems durch Antimetaboliten des Nikotinamids. Dtsch. Med. Wochenschr. **42**, 2025–2036 (1963)

Davidson, L., Lloyd, K., Dankova, J., Hornykiewicz, O.: L-DOPA treatment in Parkinson's disease: Effect on dopamine and related substances in discrete brain regions. Experientia **27**, 1048–1049 (1971)

Goldstein, J. M., Barnett, A., Malick, J. B.: The evaluation of anti-Parkinson drugs on reserpine-induced rigidity in rats. Eur. J. Pharmacol. **33**, 183–188 (1975)

Halbhübner, K., Loos, D., Herken, H.: Pharmacological and electromyographic differentiation of the neurotoxic action of 6-aminonicotinamide. Naunyn-Schmiedeberg's Arch. Pharmacol. **297**, R57 (1977)

Herken, H., Keller, K., Kolbe, H., Lange, K., Schneider, H.: Experimentelle Myelopathie – Biochemische Grundlagen ihrer zellulären Pathogenese. Klin. Wochenschr. **51**, 644–657 (1973)

Herken, H., Meyer-Estorf, G., Halbhübner, K., Loos, D.: Spastic Paresis after 6-aminonicotinamide: Metabolic disorders in the spinal cord and electromyographically recorded changes in the hind limbs of rats. Naunyn-Schmiedeberg's Arch. Pharmacol. **293**, 245–255 (1976)

Hornykiewicz, O.: Neurochemistry of Parkinsonism. In: Handbook of Neurochemistry, Vol. 7 (A. Lajtha, ed.), pp. 465–501. New York: Plenum Press 1972

Horowski, R., Wachtel, H.: Direct dopaminergic action of lisuride hydrogen-maleate, an ergot derivate, in mice. Eur. J. Pharmacol. **36**, 373 (1976)

Johnson, W. J., McColl, J. D.: 6-Aminonicotinamide, a potent nicotinamide antagonist. Science **122**, 834 (1955)

Jurna, I.: Striatal monoamines and reserpine and chlorpromazine rigidity. Pharmac. Ther. B **2**, 113–128 (1976)

Jurna, I., Lanzer, G.: Inhibition of the effect of reserpine on motor control by drugs which influence reserpine rigidity. Naunyn-Schmiedebergs Arch. Pharmak. Exp. Path. **262**, 309–324 (1969)

Kehr, W.: Effect of lisuride and other ergot derivates on monaminergic mechanisms in brain. Eur. J. Pharmacol. **41**, 261–273 (1977)

Morrison, A. B., Webster, R. A.: Drug-induced experimental Parkinsonism. Neuropharmacology **12**, 715–724 (1973)

Pletscher, A., Bartholini, G.: Selective rise in brain dopamine by inhibition of extracerebral levodopa decarboxylation. Clin. Pharmacol. Ther. **12**, 344–352 (1971)

Rinne, U. K., Sonninen, V.: A double blind study of L-DOPA treatment in Parkinson's disease. Eur. Neurol. **1**, 180–191 (1968)

Roos, B.-E., Steg, G.: The effect of L-3,4-dihydroxyphenylalanin and DL-5-hydroxytryptophan on rigidity and tremor induced by reserpine, chlorpromazine and phenoxybenzamine. Life Sci. **3**, 351–360 (1964)

Schneider, H.: Elektronenmikroskopische Befunde bei selektiven Läsionen der spinalen grauen Substanz. Untersuchungen am Modell der 6-Aminonikotinamid-Intoxikation und der temporären Ischämie. Habilitationsschr., FB klin.-theor. Med. Freie Univ. Berlin 1971

Steg, G.: Efferent muscle innervation and rigidity. Acta Physiol. Scand. **61** Suppl., 225 (1964)

Sternberg, S. S., Philips, F. S.: 6-Aminonicotinamide and acute degenerative changes in the central nervous system. Science **127**, 644–646 (1958)

Votava, Z., Lamplová, I.: Antiserotonin activity of some ergolenyl and isoergolenyl derivates in comparison with LSD and the influence of monoamine inhibition on this antiserotonin effect. In: Neuropsychopharmacology, Vol. 2 (E. Rothlin, ed.), pp. 68–73. Amsterdam: Elsevier, 1961

Wiesendanger, M.: Pathophysiology of muscle tone. Schriftenreihe Neurologie **9**, Berlin-Heidelberg-New York: Springer 1972

Wolf, A., Cowen, D.: Pathological changes in the central nervous system produced by 6-aminonicotinamide. Bull. N.Y. Acad. Med. **35**, 814–817 (1959)

Received June 29 / Accepted August 22, 1977