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Evaluation of the Central Effects of Ergot Alkaloids by Means of Electroencephalography

V.G. Longo and A. Loizzo

Laboratorio di Farmacologia, Istituto Superiore di Sanità, Roma

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Abstract. The effects of some ergot derivatives on the electroencephalogram and behavior of laboratory animals (mice, rats, rabbits) have been surveyed. The interference of bromocriptine on the dopaminergic central systems has been studied using behavioral (interference with the effects induced by *L*-dopa, 5HT, TRF or neuroleptic drugs) and electrophysiological (EEG) methods. While no clear effects of bromocriptine could be evidenced in mice, EEG recordings from the dorsal hippocampus of the rabbit showed a slight disruption of ϑ-waves after administration of 2 mg/kg i.v. of the drug or more.

Among the neuropharmacological studies carried out on ergot alkaloids, those dealing with their effects on the cerebral electrical activity are scarce. And this is particularly true if the peptide alkaloids are considered. If we go back to the literature of the fifties, namely when a sort of general EEG screening of all types of drugs was carried out in the animal, we find the reason for this scarcity: people were discouraged by the lack of effects of these drugs on the EEG. Table I presents the results of these early studies, which pointed out that these drugs do not significantly alter the EEG. On the other hand, more data are available on the EEG effects of the natural and semisynthetic amine alkaloids, some of which have dramatic effects on the psyche.

Like many other neuropharmacologists working with psychoactive drugs, we presume to have convenient methods by which the effects observed in man can be demonstrated in laboratory animals. Therefore, some time ago, we studied in the rabbit the relationships between psychodysleptic action and EEG alterations in a series of amine derivatives of lysergic acid. The rabbit was chosen because early EEG investigations (*Delay et al.*, 1952) pointed out some characteristic alterations induced by LSD, namely a flattening of the voltage of the electrocorticogram and a disruption of the ϑ-

Table I. Effects of peptide ergot alkaloids on the EEG

	Animal used	Dose applied	Outcome	Reference
Ergotamine	cat	1 mg/kg i.v.	no effect	*Exley et al.*, 1958
	cat	0.02 mg i.c.	no effect	*Schwartz et al.*, 1956
DH-ergotamine	cat	1 mg/kg i.v.	arousal	*Exley et al.*, 1958
	rabbit	1 mg/kg i.v.	no effect	*Goldstein and Muñoz*, 1961
	rabbit	2 mg/kg i.v.	no effect	*Longo*, 1962
Hydergine	rabbit	0.1 mg i.c.	sleep	*Cahn et al.*, 1954
Bromocriptine	rat	0.06 mg i.c.	no effect	

Table II. Data of the effects of several lysergic acid derivatives on the EEG (*Longo and Bovet*, 1964) are compared to the hallucinogenic action in man as reported by *Isbell et al.* (1959); the drugs which induce hallucinations and mental disturbances in humans alter the EEG at minute doses

Code	Compound	Hallucinogenic LSD = 100	Rabbit EEG disruption of hippocampal waves
LSD	*d*-lysergic acid diethylamide	100	0.02
LPD	*d*-lysergic acid pyrrolidide	10	0.025
LAE	*d*-lysergic acid monoethylamide	5	0.025
Ergometrine	*d*-lysergic acid propanolamide	?	0.5–1
Methylergometrine	*d*-lysergic acid butanolamide	?	0.5–1
BOL	2-brom lysergic acid diethylamide	<2	>2
UML	*l*-methyl lysergic acid butanolamide	0	>3
l-LSD	*d*-isolysergic acid diethylamide	0	>3

rhythm recorded from the dorsal hippocampus. An example of these EEG changes in presented in figure 1.

Table II shows the results obtained: EEG alterations at the level of the hippocampus are induced only by the drugs which demonstrate a psychodysleptic activity in man.

Concerning the mechanisms by which these changes are induced, much importance has been given on the effects of these drugs on the serotonergic central system. And this not so much in the sense of an antiserotonin action, as was originally proposed on the basis of data obtained in the isolated organ, but rather envisaging the central effects of these drugs as resulting from stimulation of the serotoninergic system (*Verdeaux and Longo*, 1977).

We have carried out in our laboratory an EEG screening of 2-bromo-α-ergocryptine (bromocriptine, CB 154) in chronically implanted rabbits and rats. The drug is scarcely active on the EEG of the rabbit, and up to 10 mg/kg i.v. does not give rise to activation of the EEG such as observed after administration of amphet-

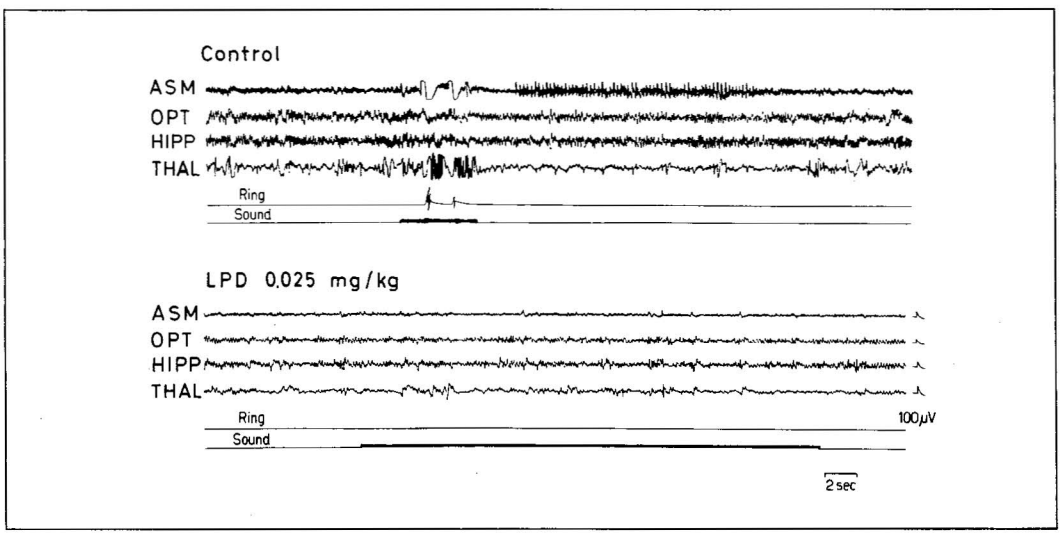

Fig. 1. Effects of lysergic acid pyrrolidide (LPD) on EEG and on instrumental reward discrimination. After administration of 0.025 mg/kg of the drug, there is the blocking of the performance of the exercise, together with the flattening of the tracing and disruption of the ϑ-waves of the hippocampus. ASM = Anterior sensorimotor cortex; OPT = optic cortex; HIPP = dorsal hippocampus; THAL = anteromedial nuclei of the thalamus. For details see *Longo and Bovet* (1964).

amine in much lower doses (1–2 mg/kg) or of *L*-dopa (20–40 mg/kg). The recordings from the dorsal hippocampus are not modified after administration of doses up to 2 mg/kg i.v.; with higher doses we have noticed a slight disruption of the waves.

CB 154 was administered to rats via a permanent cannula reaching the lateral ventricle. No appreciable EEG effects were induced by the drug in doses up to 0.06 mg.

Passing now to the second task, we feel that some of the data presented in the course of this workshop lead us to a better understanding of some aspects of the mechanism of action of ergot alkaloids. We are all aware that the pharmacology of the ergot alkaloids is complex, and since the beginning it appeared difficult to disentangle the various effects of the ergot derivatives. Of the wide array of actions of these compounds, emphasis has been placed until a few years ago on their sympatholytic and smooth muscle effects. Recent investigations have brought to attention other important properties which were until now overlooked, and among them some effects attributed to stimulation of central dopaminergic receptors; these effects are particularly evident for the bromo-α-derivative of ergocryptine. Of course, reading back the literature on the pharmacology of the ergot alkaloids, one can find several hints to this dopaminergic component. Just to quote a few: the mechanism of the emesis induced by the dihydrogenated and non dihydrogenated peptide alkaloids has been reported to a stimulation of the chemoreceptor trigger zone, very similar to that exerted by apomorphine. Stereotyped behavior was described by *Schwartz et al.* (1956) in cats treated with 20 μg of ergotamine injected intraventricularly, as well as by *Stone* (1973) in rats receiving 1–2 mg/kg parenterally of agroclavine. Not to mention the reports of *Shelesnyak* (1954)

which evidenced an effect of ergotoxine on the central neuroendocrine regulator systems.

Since various hypothalamic releasing factors have been chemically identified as oligopeptides, one would be tempted to attribute the neuroendocrine effects of some ergot derivatives to the peptidic moiety of the molecule. Strangely enough, these effects seem common to most of the ergot alkaloids, either aminic, peptidic or dihydrogenated (*Pieri et al.*, 1975; *Pijnenburg et al.*, 1973). Since a potentiating effect of some oligopeptides on the behavioral effect of *L*-dopa and 5-hydroxytryptophan in mice has been described (cf. for references *Huidobro-Toro et al.*, 1975) we have searched such an activity in CB 154. From our results it seems that CB 154 (up to 10 mg/kg i.p.) does not influence the behavioral symptoms elicited by *L*-dopa (100 mg/kg i.p.) or 5-hydroxytryptophan (75 mg/kg i.p.) in pargyline-pretreated mice. It seems therefore that all these alkaloids possess a dopaminergic moiety, which is responsible for the neuroendocrine effects.

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Dr. V.G. Longo, Laboratorio di Farmacologia, Istituto Superiore di Sanità, Roma (Italy)