Primate Cerebral Synaptic Inhibition by Drugs.* (30619)

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Comparative neuropharmacology can go beyond pragmatic opportunism to provide an instructive display of unifying similarities and clarifying differences among the species as they approach man in cerebral development. Accordingly, our previous findings that the cerebral synaptic inhibition produced by substances natural to the brain, like serotonin, and by drugs, like lysergic acid diethylamide (LSD-25) could be obtained in cats(1) and dogs(2) coupled with the similar results of Slocombe, Hoagland and Tozian in rats(3) have led us to examining a subhuman primate in tracing the possible relation to actions in man.

Methods and results. The postsynaptic potentials evoked by submaximal stimuli serve as a sensitive and accurate index of synaptic transmission and the close-arterial injection as the means of producing a change in the chemical environment that is largely confined to the cerebral region under study(4). Utilizing the transcallosally evoked cortical potential and intracarotid injection in the lightly pentobarbitalized spider monkey, we find that serotonin and LSD-25 exercise cortical synaptic inhibitory actions as indicated by the reduction of the evoked response (Fig. 1). These findings are qualitatively identical with those we have previously described in the cat and dog and the doses for the monkey are in the same range as for the cat. A test of specificity is provided by the protection afforded by chlorpromazine (CPZ)(1) (Fig. 2). The available data gathered in Table I show a similarity of synaptic action which is paralleled in the case of LSD-25 by corresponding behavioral data *viz.*, increased response latency, decreased differentiation and increased number of intersignal responses, indicating an inhibition of behavior (including inhibition of inhibition or disinhibition) that agrees with the synaptic inhibition that would seem to underlie it. It remains to be seen whether the parallelism is good enough so that filling in the gaps in the table will not reveal any major inconsistencies.

Comments. Thus, comparative neuropharmacological studies on serotonin and LSD-25 suggest that the actions and mechanisms observed are not unique characteristics of certain species, but apply generally in such a series as this and probably extend to man. This conclusion is strengthened by the increasing behavioral susceptibility to LSD-25 that we have previously described, as one ascends the evolutionary scale represented by this series and as one increases the complexity of the behavioral paradigm(12). The value of a comparative neuropharmacological approach in suggesting significant similarities and the further data required to test the consequent implications (Table I) are made evident.

Summary. Cortical evoked potential studies

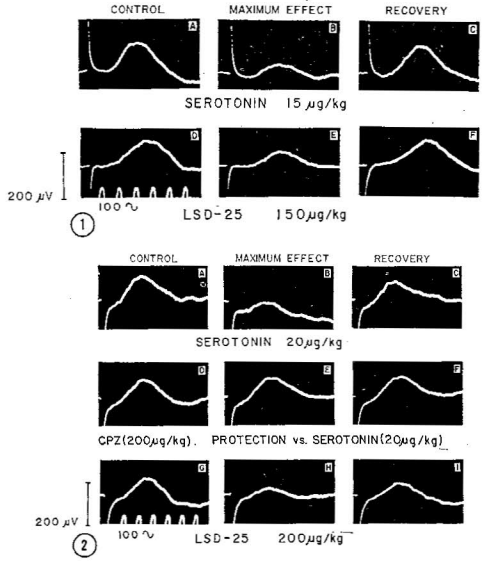

FIG. 1 and 2. Primate cerebral synaptic inhibition by drugs in an intercortical (transcallosal) system. Potentials evoked in cerebral cortex. Electrical stimulation contralateral cortex every 2 sec. Injections in ipsilateral common carotid artery. Spider monkey. Pentobarbital 30 mg/kg.

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TABLE I. Comparative Neuropharmacology.

Species	Mode	Serotonin	LSD-25	CPZ protection *vs*
Rat	Synaptic*	Inhibition (3)		
	Behavioral		C.Ap.L. ↑ (1, 5) C.Av.L. ↑ (1, 5) Diff. ↓ (1, 5, 6) Intersignal responses ↑ (6)	LSD-25 on C.Ap.
Cat	Synaptic	Inhibition (1)	Inhibition (1)	Serot. (1); LSD-25 (1, 7)
	Behavioral		Intersignal responses ↑ (6) (No. of responses)	
Dog	Synaptic	Inhibition (2)	Inhibition (2)	
Monkey	Synaptic	Inhibition	Inhibition	Serot.; LSD-25
	Behavioral		C.Ap.L. ↑ (8) Diff. ↓ (8) Intersignal responses ↑ (8)	LSD-25 on C.Ap. (8)
Man	Synaptic		Inhibition (9)	
	Behavioral		Hallucination (10, 11) Perceptual association ↓ (12)	LSD hallucination (10, 11)

↑, increased; ↓, decreased; C.Ap.L., conditioned approach latency; C.Av.L., conditioned avoidance latency; Diff., differentiation (tone or time).

* Synaptic in this table refers to transcallosally [except(9)] activated cortical synapses. However, as indicated in the table of "Generality of Cerebral Synaptic Drug Response" that we have published(12), synaptic inhibition by serotonin and LSD-25 is obtained at a variety of cerebral synapses, including cortical, subcortical and brain-stem.

show that the synaptic inhibition by serotonin and lysergic acid diethylamide observed in the rat, cat and dog can also be obtained in the monkey. Specificity of action is indicated by the protection afforded by chlorpromazine. Comparison of the synaptic and behavioral effects suggests an orderly, parallel relation in a series that progresses through a subhuman primate to man.

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