Actions of Chlorpromazine and of Reserpine on Spinal Reflex Activity in the Cat. (23383)

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These experiments are based on the finding that doses of chlorpromazine that do not modify conduction depress transmission in the inferior mesenteric ganglion of the cat (Krivoy, unpublished). If the synapse in the spinal cord resembles the ganglionic synapse, chlorpromazine should modify transmission in the spinal cord also. The present experiments were designed to study this possibility.

Methods. In one preparation(1), laminectomy was performed at the level of the last lumbar or first sacral segment to expose homolateral dorsal and ventral roots from the same spinal segment. The roots were mounted on electrodes. The skin edges around the incision were elevated and the trough so formed was filled with mineral oil maintained at 37°C. A second method(2) consisted of stimulating and recording through 2 pairs of electrodes applied to the same sciatic nerve, which had been cut distally. Electrical equipment and methods of recording have been described previously(3), only the AC amplifier being used in these experiments. Bright silver electrodes were used with spinal roots, whereas wick electrodes were used for sciatic nerve experiments. The dorsal root or sciatic nerve was stimulated with biphasic pulses at a frequency varying from .5-1/sec. with a stimulus duration of .1-.5 msec. Except where noted, stimulus intensity was 50-80% maximal. All stimulus parameters were maintained constant throughout any given experiment.

Decerebration was performed at the level of the superior colliculus under ether. Ether was stopped at least 2 hours before the experiment. Intact cats were anesthetized with pentobarbital sodium, 30 mg/kg i.p. Blood pressure was recorded from a carotid artery in the spinal root preparation and from the contralateral femoral artery in the sciatic nerve experiments. Cats with blood pressures below 120 mm Hg prior to drug administration were not used. Administration of reserpine or chlorpromazine was delayed for at least one hour after the surgical procedures and the placing of electrodes.

Chlorpromazine and reserpine were administered as solutions: 1. chlorpromazine, 2.5 g, ascorbic acid, .2 g, sodium bisulfite, .1 g, sodium sulfite, .1 g, sodium chloride, .6 g, and water, q.s. to 100 cc; 2. reserpine, .25 g, benzyl alcohol, 2 cc, citric acid, .25 g, propylene glycol, 10 cc, and distilled water, q.s. to 100 cc. Control experiments consisted of administration of the above solvents without active agents. In experiments to test the effect of cardiovascular collapse on spinal activity, animals were bled to death by section of one carotid artery.

Results. I. Stability of the preparation. Fig. 1 was prepared from a spinal root preparation to which only nembutal was administered. In the insert, records representative of the 2 types of preparations (sciatic nerve and spinal root) are shown. Essentially identical results were obtained in 8 experiments of this type. The monosynaptic reflexes were stable for prolonged periods of time. Although the polysynaptic reflexes were more variable, they also showed no consistent deterioration during the period of observation.

II. Anesthetized Cat. A. Chlorpromazine. Fig. 2A illustrates the data of an experiment typical of 12. Although both mono- and

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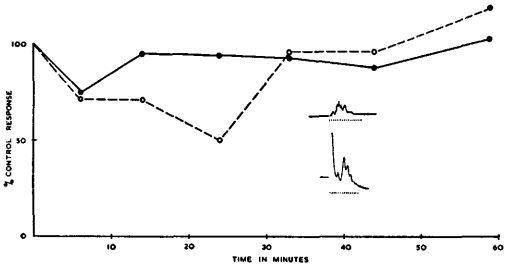

FIG. 1. Stability of monosynaptic spinal reflexes for long times. Solid line—monosynaptic activity; dotted line—polysynaptic. Data used in these graphs were from a spinal root experiment. Inserts: Upper tracing from a spinal root experiment; lower tracing from sciatic nerve preparation. Tracings used in inserts are typical. Time signal—1000 cycles.

polysynaptic activities were decreased by the drug, monosynaptic activity suffered first. The stimulus used in Fig. 2A was submaximal. When a supramaximal stimulus was used, spinal activity was modified by chlorpromazine to a considerably lesser extent. Fig. 2B shows the results obtained with supramaximal stimulation from the same preparation used for Fig. 2A. Although an effect from chlorpromazine was evident almost immediately, maximal action was not achieved for several minutes with supramaximal stimulation. The *minimal dose* of chlorpromazine necessary to decrease the response of the spinal root preparation was approximately .2 mg/kg intramuscularly or intravascularly. When the sciatic nerve preparation was used, the dose required was approximately 2-3 mg/kg. *B. Reserpine.* Results obtained with reserpine were essentially the same as those with chlorpromazine, except that there appeared to be

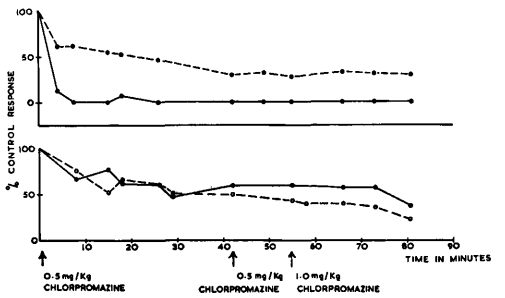

FIG. 2. Influence of chlorpromazine on mono- and polysynaptic activities in anesthetized spinal root preparation stimulated submaximally (upper graph) or supramaximally (lower graph). Solid line—monosynaptic activity; dotted line—polysynaptic.

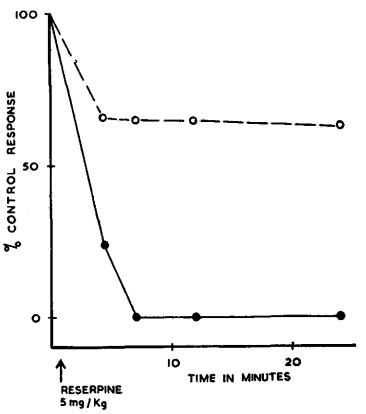

FIG. 3. Actions of reserpine on mono- and polysynaptic activities of spinal root preparation. Solid line—monosynaptic activity; dotted line—polysynaptic.

greater specificity for monosynaptic activity. Fig. 3, typical of 9 experiments, shows an example of the effects of reserpine. Since small doses of reserpine do not act immediately, no attempt was made to determine the minimal effective dose of this drug.

III. Decerebrate Cats. A. Chlorpromazine. Chlorpromazine in the decerebrate cat had the same action as in the anesthetized preparation, except that the specificity for monosynaptic activity was more conspicuous. Fig. 4 is typical of 11 such experiments. *B. Reserpine.* In 9 experiments, reserpine had the same actions in the decerebrate cat as those observed in the anesthetized animal. *IV. Induced cardiovascular collapse.* When cardiovascular collapse was induced by bleeding in

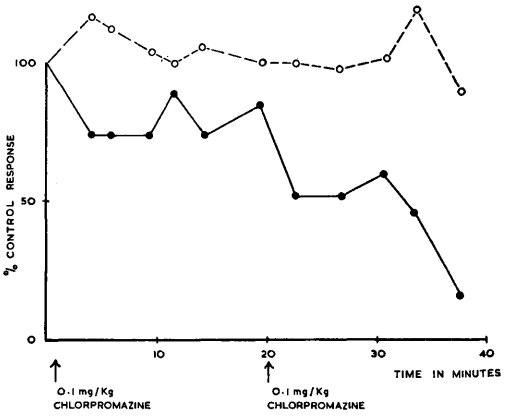

FIG. 4. Actions of chlorpromazine in the decerebrate cat. Data from a sciatic nerve preparation. Solid line—monosynaptic activity; dotted line—polysynaptic.

the absence of drugs, polysynaptic activity was depressed before monosynaptic activity was affected. In fact, monosynaptic activity frequently was enhanced as an initial response to bleeding. This information results from 6 experiments. *V. Controls.* Although the reserpine vehicle alone frequently augmented monosynaptic activity initially, neither the chlorpromazine vehicle nor the reserpine vehicle produced depression similar to those described in Section I. A total of 12 experiments was performed, 5 with the reserpine vehicle. *VI. Blood pressure.* Although both chlorpromazine and reserpine lowered blood pressure, this effect bore no temporal relationship to the actions of the drugs on the induced potentials.

Discussion. These results support the conclusions that, under the conditions of these experiments, chlorpromazine and reserpine inhibit spinal reflexes and that both have strong specificity for monosynaptic systems. Angelucci(4) has reported that both chlorpromazine and reserpine inhibit spinal reflexes in the frog; Dasgupta and Werner(5) found that chlorpromazine completely suppresses the crossed extensor reflex in decerebrate cats. On the other hand, Preston(6) has reported that doses of chlorpromazine causing obvious changes in the behavior of cats produce no observable alterations in monosynaptic and polysynaptic reflex arcs of the spinal cord; doses of 5 mg/kg of reserpine were found to increase the magnitude of the monosynaptic spike of the ventral root potential without significant change in the polysynaptic potentials(7). Our results fall between these two extremes: we find that both chlorpromazine and reserpine decrease fairly specifically the magnitude of the monosynaptic potential, which would be expected to mean that these drugs inhibit simple reflexes like the knee jerk but not more complex ones. The ultimate causes of the differences between the authors cited and between certain of these and ourselves are not apparent. Differences in technic may play an important part. If our conclusion that chlorpromazine and reserpine are relatively specific for monosynaptic reflex arcs is correct, this finding would be presumptive evidence for the existence of 2 physicochemical mechanisms in the spinal cord, one associated with monosynaptic activity and the other with polysynaptic activity. Such duality of mechanisms has been postulated by Holmstedt and Skoglund(8). These experiments support also the conclusion of Schneider(9) that reserpine leaves efferent activity practically intact even though it blocks the reflex arc. The concept that inhibition of spinal reflex activity by chlorpromazine and reserpine is a consequence of systemic cardiovascular collapse is ruled out by the finding that polysynaptic activity is more sensitive than monosynaptic to surgical shock.

Summary. 1. Chlorpromazine and reserpine inhibit spinal reflex activity. 2. The inhibition affects predominantly monosynaptic reflex pathways when submaximal stimuli and minimal doses of chlorpromazine or of reserpine are used. 3. The spinal effects of chlorpromazine and reserpine do not result from circulatory changes, unless these be local alterations in the circulation within the spinal cord. That possibility has not been studied.

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