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EFFECTS OF CHLORPROMAZINE ON SPINAL CORD REFLEX MECHANISMS*†

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Summary—The effects of chlorpromazine (CPZ) on the patellar reflex and segmentally evoked spinal cord potentials were determined in the high spinal and hemisectioned spinal cat preparations. CPZ in doses of 1–32 mg/kg given intravenously (as an accumulative dose) produced no statistically significant alteration of the patellar reflex and segmentally evoked monosynaptic potentials. The segmentally evoked polysynaptic potential was significantly depressed (1–32 mg/kg). CPZ was shown to cause a significant depression of facilitation and inhibition of the patellar reflex produced by electrical stimulation of the lateral and ventral funiculi of cervical cord segments 1 and 2. Facilitation of the patellar reflex produced by contralateral stimulation of the sciatic nerve was resistant to doses of CPZ but was significantly depressed by 4 mg/kg. Patellar reflex inhibition produced by ipsilateral sciatic nerve stimulation was never observed to be depressed by doses used in this study. The patellar reflex recorded ipsilateral to a high cervical (C1) and mid-thoracic (T6) hemisection of the spinal cord was resistant to doses of CPZ (1–8 mg/kg) while the contralateral patellar reflex was depressed. The mean arterial blood pressure was significantly elevated by doses of CPZ (4–32 mg/kg). The evidence presented indicates the internuncial neuron of the spinal cord as a probable site of chlorpromazine action. Possible mechanisms of blood pressure elevation are discussed.

INTRODUCTION

SEVERAL investigators have demonstrated that chlorpromazine (CPZ) exerts a motor depressant effect on the brainstem reticular formation (DASGUPTA and WERNER, 1955; KREINDLER *et al.*, 1958; KRUGLOV, 1958; SILVESTRINI and MAFFII, 1959; VALDMAN, 1962; and HUDSON and DOMINO, 1963, 1964). It has been further demonstrated that CPZ produces a significant depression of the mesencephalic facilitatory area of the brainstem reticular formation coupled with a lesser depression of medullary inhibitory area (KRUGLOV and SINITSYN, 1959; HUDSON and DOMINO, 1963). These conclusions gain support from the observation that some motor reflexes are apparently very resistant to doses of CPZ in the high spinal animal (PRESTON, 1956; HENATSCH and INGVAR, 1956; BEIN, 1957; KRUGLOV, 1958; SILVESTRINI and MAFFII, 1959; and KRYLOV, 1960).

Such reflex depression in the intact but not the spinal animal suggests that the depression is related to a CPZ effect on a neurogenic influx present during the intact state of the neuroaxis and absent when it is sectioned. However, CPZ could have an effect anywhere along this path. Thus in addition to a brainstem site of action, CPZ could be acting at a spinal cord level to inhibit a flow of impulses originating from supraspinal structures.

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Spinal cord section under these circumstances would preclude supraspinal driving influences and prevent the observation of such a possible effect.

HENATSCH and INGVAR (1956) reported that CPZ produced moderate and superficial reductions of efferent γ motor impulses in the spinal animal. On the basis of this observation these investigators postulated a possible spinal cord action of CPZ. It was later demonstrated (SCHULTE and HENATSCH, 1958) that the tonic discharge of α and γ motoneurons following spinal transection could be promptly depressed by CPZ. BUSCH *et al.* (1960) using the spinal preparation also demonstrated that the tonic discharge of α motoneurons to muscle stretch was completely inhibited or converted to a phasic discharge by 1 mg/kg of CPZ given intravenously. The same dose of CPZ was shown to abolish reflexly activated γ motoneuron discharge. The reports of DE SALVA and OESTER (1960) and HERMAN and BARNES (1964) further indicate an effect of CPZ directly on the spinal cord.

The purpose of the present investigation is to elucidate further the effects of CPZ on spinal cord motor mechanisms.

METHODS

Experiments with mechanically recorded reflexes

Sixty-six adult cats of both sexes ranging from 2·0 to 3·4 kg were used. Surgical operation was performed under pentobarbital-sodium (35 mg/kg i.p.) or diethyl-ether anesthesia. The animals were suspended in a Horsley–Clarke stereotaxic apparatus and the patellar reflex elicited once per second via a mechanically operated hammer. The isometric reflex contractions were recorded on a Grass polygraph. Body temperature was maintained thermostatically and carotid artery blood pressure was monitored in all animals. Three variations of this basic preparation were used: (a) pentobarbital anesthetized high spinal (C1) cats with acutely implanted electrodes in cervical cord segments, (b) unanesthetized high spinal (C1) cats with acutely implanted cortical recording electrodes and bilateral sciatic nerve stimulating electrodes, and (c) pentobarbital anesthetized cats with a spinal hemisection (C1 or T6) and acutely implanted stimulating electrodes in the spinal cord and reticular formation. A few animals were hemisectioned and allowed to recover 7 days prior to experimental use.

In group (a) bipolar concentric electrodes were acutely implanted in the lateral and ventral funiculi of cervical cord segments 1 and 2. Electrode positions were chosen on the basis of the response of the patellar reflex to cord stimulation. A pulse width of 1 msec and a frequency of 100 c/s were used. The stimulus was applied for 5 sec. Electrolytic lesions were made to mark areas of stimulation. Histologic sections were made for localization of active sites.

In group (b) experiments were commenced 3–4 hr following spinal cord transection and cessation of ether administration. The electroencephalogram (EEG) was recorded bipolarly between the two hemispheres in the area of the pericruciate motor cortex. Facilitation of the patellar reflex was produced by stimulation of the contralateral sciatic nerve at high frequencies (120 c/s) and inhibition by high frequency (120 c/s) stimulation of the ipsilateral sciatic nerve. The stimulus was applied for 10 sec.

In group (c) the patellar reflex was recorded bilaterally. Facilitation and inhibition of this reflex was elicited by electrical stimulation of the medullary and mesencephalic reticular formation contralateral to the hemisection and by stimulation of the cervical cord ipsilateral and caudal to the hemisection. The hemisection was always made on the

right side of the spinal cord at C1 or T6. The electrodes were positioned in the brainstem with a Horsley–Clarke stereotaxic apparatus (for details see HUDSON and DOMINO, 1963). A pulse width of 1 msec and a frequency of 100 c/s was used for stimulation of the brainstem areas and the spinal cord. Stimulus was applied for 5 sec.

All animals were artificially respired at a rate of 18 strokes/min and a tidal volume of 50–70 ml. CPZ was administered intravenously on an accumulative dose schedule at 10 min intervals.

Experiments with acute dorsal-ventral root preparations for recording monosynaptic and polysynaptic potentials

Under open drop ether anesthesia a spinal laminectomy was performed at the lumbosacral level for intradural isolation of the ipsilateral dorsal and ventral roots of segment L7 or S1. Wound edges were infiltrated with 2% lidocaine containing 0·001% epinephrine (E). The spinal cord was sectioned at the level of the allanto-occipital membrane. The animal was placed on artificial respiration and immobilized with D-tubocurarine. A pool of warm mineral oil was placed above the spinal cord and the temperature adjusted between 37–38°C. The reproducibility of the reflex was determined during a period of 1–3 hr following surgical operation. This period also allowed recovery from ether anesthesia. The dorsal root was stimulated with square wave pulses of 0·96–1·8 V of a duration of 0·5 msec, at a frequency of 2 c/s. A sweep speed of 2 msec/cm and a delay of 5 msec were used. The distal end of the ventral root was crushed to produce monophasic spike potentials. The electrical responses were amplified and photographed from the cathode ray oscilloscope with a Grass camera (model C4).

RESULTS

Effects of CPZ on the patellar reflex and mean arterial blood pressure of the high spinal pentobarbital anesthetized cats

In 10 high spinal cats doses of CPZ increasing from 1 to 16 mg/kg given intravenously produced an initial fall in the blood pressure which gradually recovered and stabilized at a point above control levels. The depressor component of this diphasic response could be greatly attenuated by a decrease in the rate of injection. The accumulative dose of 4–16 mg/kg caused a statistically significant increase in the mean arterial blood pressure ($P>0·001$).

The increase in the mean arterial blood pressure had a gradual onset but was obviously present during the 10 min interval between doses. The increase in blood pressure was paralleled by an enhancement in the amplitude of the patellar reflex (Fig. 1). Marked variability was observed in this enhancement of the patellar reflex. In spite of a sizeable increase in some preparations, the paired comparison student 't' test showed that these results were not statistically significant. Patellar reflex depression was never observed in response to doses of 1–16 mg/kg. Doses of 32–64 mg/kg, however, caused a decrease in the mean arterial blood pressure and a subsequent depression of the patellar reflex. When these doses were administered slowly they were much less effective in yielding a reduction of blood pressure and the patellar reflex.

In order to test whether the elevation of mean arterial blood pressure was time or dose related an additional 8 animals were prepared in which large effective doses of CPZ (4–32 mg/kg) were administered. These doses of CPZ produced a significant ($P>0·001$)

FIG. 1 Effects of CPZ on the patellar reflex, evoked facilitation (CF), and inhibition (CI) in the C1 cord sectioned cat anesthetized with pentobarbital. The patellar reflex was elicited by mechanically tapping the patellar tendon once per second. B.P. measured in mm Hg, patellar reflex in gram force. Time interval, B.P., force of contraction and stimulus intensities are indicated.

Panel A — Control record. Enlargement of baseline indicates period of stimulation. Following cessation of stimulation of CF note second phase of facilitation. Note rebound facilitation following stimulation of CI.

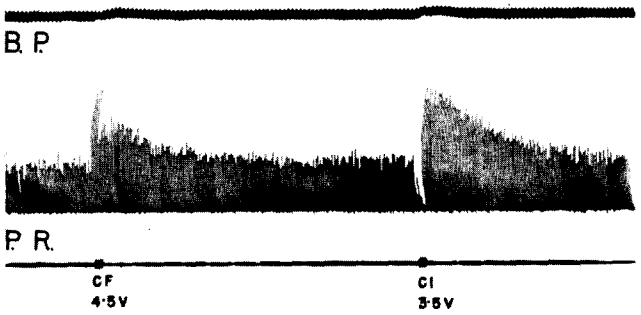
Panel B — 1·0 mg/kg of CPZ given intravenously.

Panel C — 2·0 mg/kg of CPZ given intravenously as an accumulative dose 10 min later.

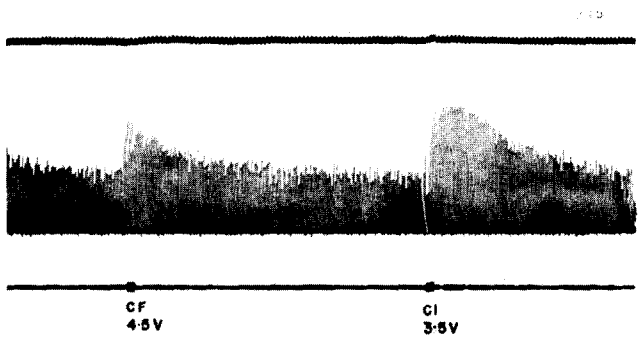
Panel D — 4 mg/kg of CPZ given intravenously as an accumulative dose another 10 min later. CI and CF stimulation sequence reversed.

Panel E — 8 mg/kg of CPZ given intravenously as an accumulative dose another 10 min later.

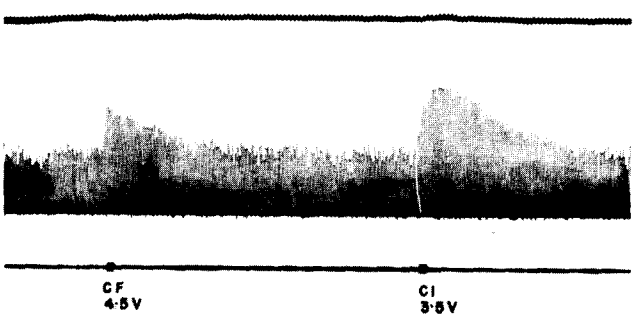
Panel F — 16 mg/kg of CPZ given intravenously as an accumulative dose another 10 min later.



A. CONTROL

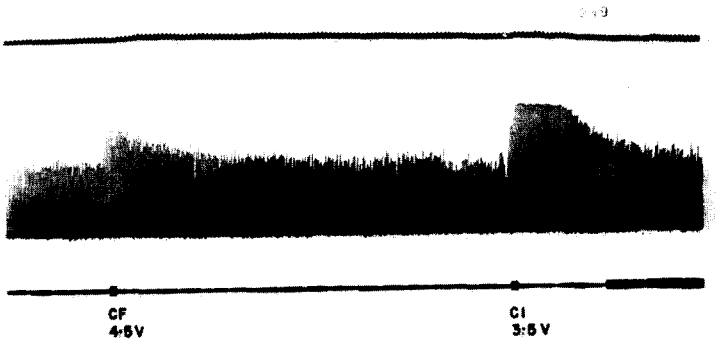


B. 1·0 mg/kg

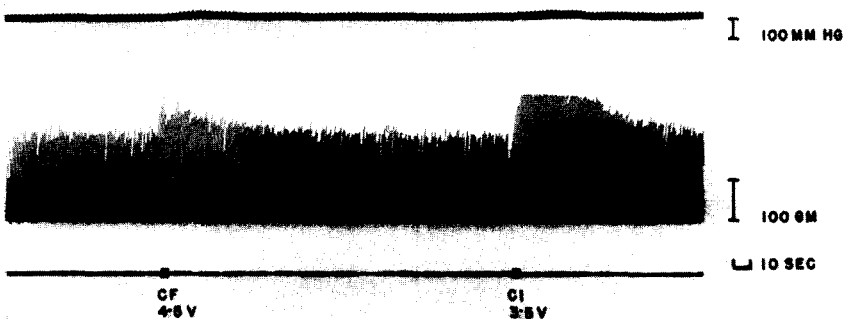


C. 2·0 mg/kg

D. 4·0 mg/kg



E. 8·0 mg/kg



F. 16·0 mg/kg

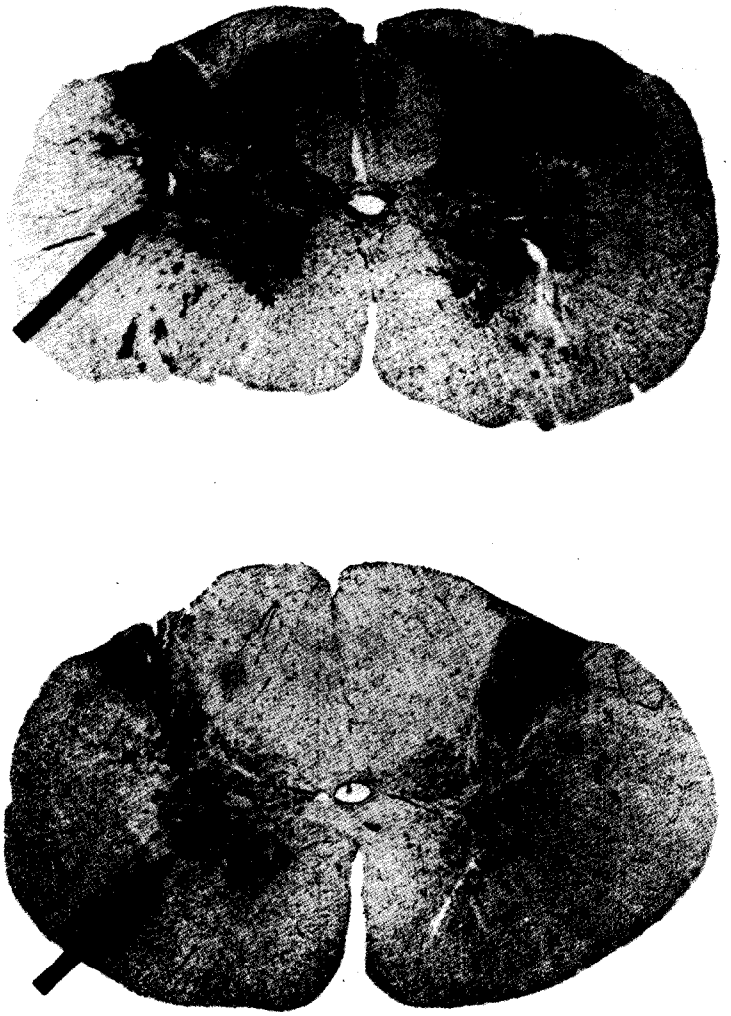
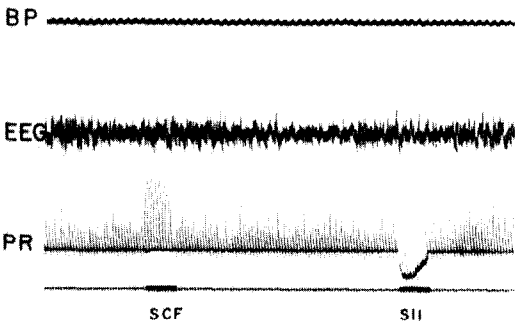


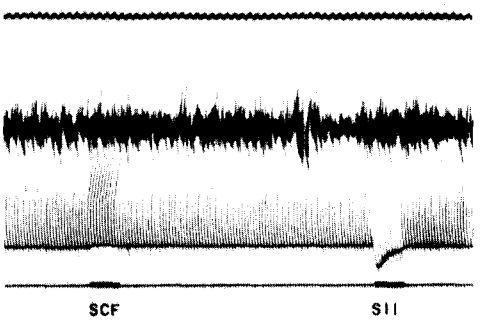
FIG. 2. Histological section from C1 cord segment, 30 μ in thickness. Stained with thionin for observations of nuclear masses. Sites of stimulation marked by electrolytic lesions at ends of arrows.

Panel A — site of reflex facilitation (CF).

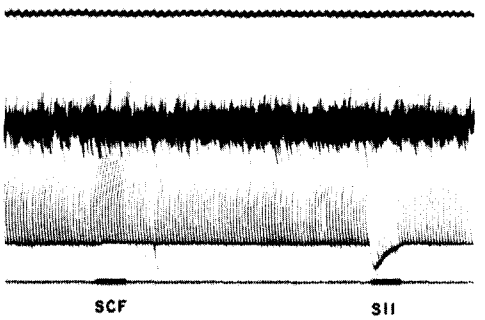
Panel B — site of reflex inhibition (CI).



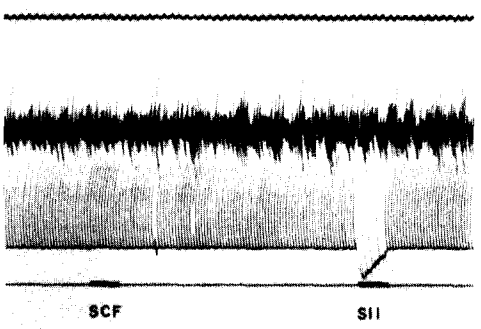
A. CONTROL



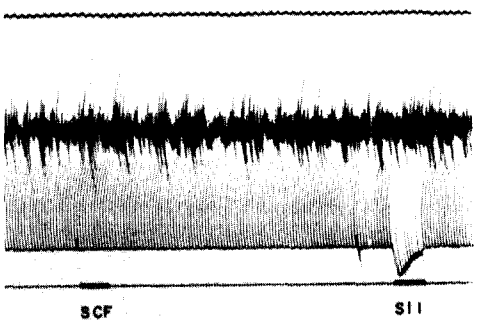
B. 1·0 mg/kg



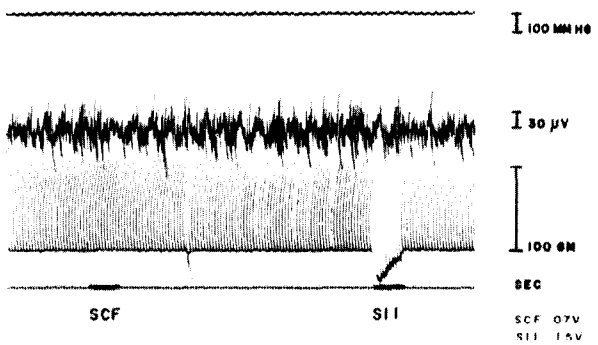
C. 2·0 mg/kg



D. 4·0 mg/kg



E. 8·0 mg/kg



F. 16·0 mg/kg

FIG. 4. Effects of CPZ on the patellar reflex, sciatic contralateral facilitation (SCF), sciatic ipsilateral inhibition, pericruciate motor cortical EEG in the C1 cord sectioned unanesthetized cat. The patellar reflex was elicited by mechanically tapping the patellar tendon once/sec. B.P. measured in mm Hg, EEG measured in μV amplitude, patellar reflex measured in gram force. Time interval, B.P., force of contraction and stimulus intensities are indicated.

Panel A — Control record.

Panel B — 1·0 mg/kg of CPZ given intravenously.

Panel C — 2·0 mg/kg of CPZ given intravenously as an accumulative dose 10 min later.

Panel D — 4 mg/kg of CPZ given intravenously as an accumulative dose another 10 min later.

Panel E — 8 mg/kg of CPZ given intravenously as an accumulative dose another 10 min later.

Panel F — 16 mg/kg of CPZ given intravenously as an accumulative dose another 10 min later.

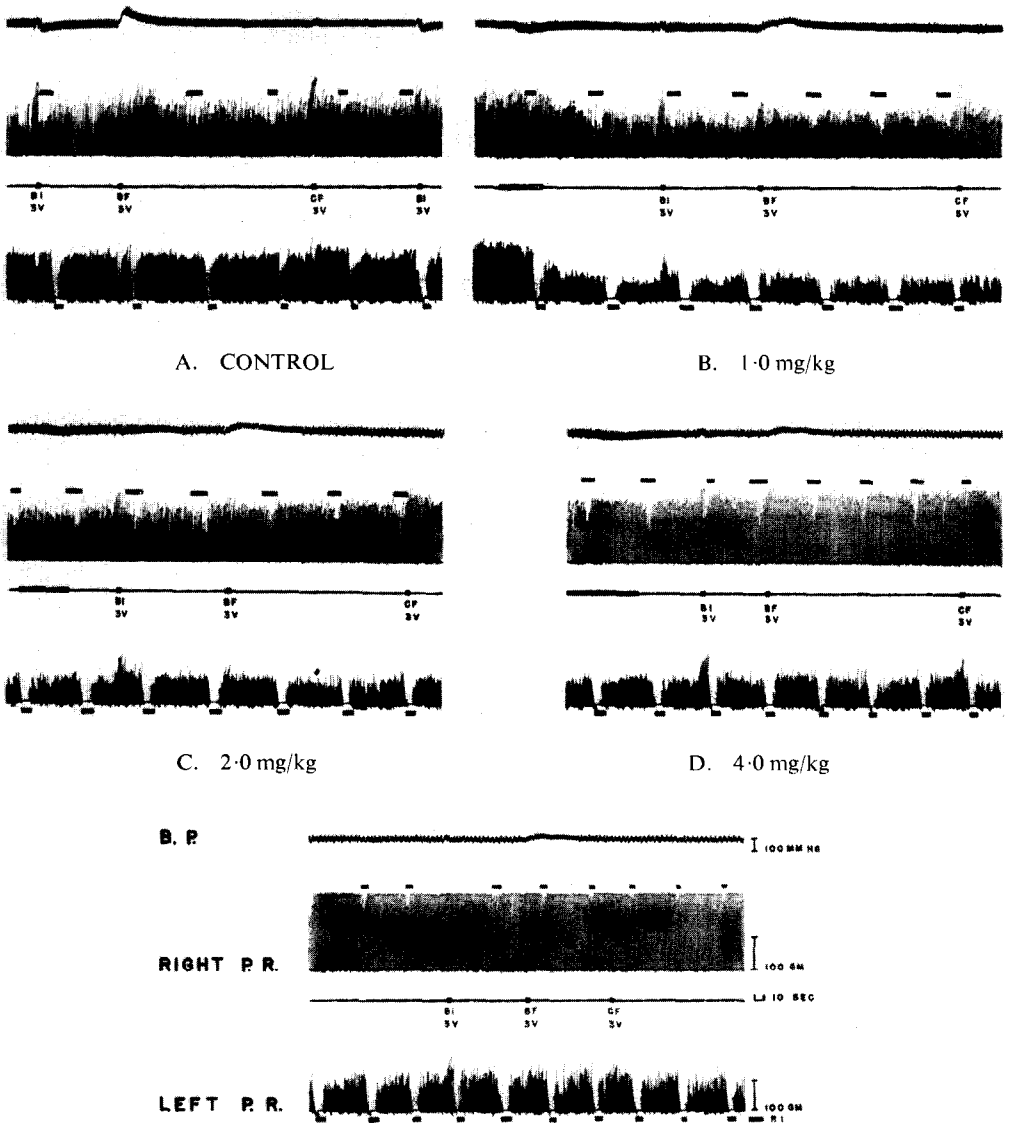


FIG. 5. Effects of CPZ on the patellar reflexes of both hindlimbs, facilitation elicited by stimulation of mesencephalic reticular formation (BF), and spinal cord (CF). Inhibition elicited by stimulation of the medullary reticular formation (BI). Reciprocal inhibition (RI) indicated by black markers above and below each patellar reflex trace. Reciprocal inhibition produced by periodic synchrony of reflex hammers used for elicitation of the patellar reflex. Animal is anesthetized with pentobarbital and the spinal cord has been hemisectioned at a C1 level on the right side. Force of contraction, B.P., time interval and stimulus intensities indicated.

Panel A — Control record.
Panel B — 1·0 mg/kg of CPZ given intravenously.
CPZ administration indicated on time line at the beginning of panels B–D by heavy black marker.
Panel C — 2·0 mg/kg of CPZ given intravenously as an accumulative dose another 10 min later.
Panel D — 4·0 mg/kg of CPZ given intravenously as an accumulative dose another 10 min later.
Panel E — 8·0 mg/kg of CPZ given intravenously as an accumulative dose another 10 min later.

elevation of the mean arterial blood pressure earlier in time than smaller amounts, suggesting a dose related effect.

Effects of CPZ on spinal cord evoked inhibition and facilitation of the patellar reflex

CPZ was administered to pentobarbital anesthetized cats which had acutely implanted bipolar concentric electrodes in cervical cord segments 1 and 2. Areas were located in the lateral and ventral funiculi which produced facilitation (CF) and inhibition (CI) of the patellar reflex respectively (Fig. 2). This functional localization of facilitatory and inhibitory spinal pathways has been demonstrated by NEIMER and MAGOUN (1947). The patellar reflex was responsive to both ipsilateral and contralateral cord stimulation indicating facilitatory and inhibitory fiber crossings at spinal levels.

Pressor and depressor responses were frequently observed in response to stimulation of CI and CF areas of the spinal cord. However, there was no consistent relationship between these parameters indicating some heterogeneity in distribution of fibers at this level.

Accumulative doses of CPZ (1–16 mg/kg) given intravenously produced a statistically significant depression of evoked inhibition ($P<0{\cdot}05$). Facilitation was either progressively depressed or obscured by the gradual increase in the amplitude of the patellar reflex (Fig. 1, panels A–F). No such changes were observed in saline control preparations. Post-inhibitory facilitation was observed to be enhanced in amplitude and prolonged in duration with increasing doses of CPZ. Panels C through F (Fig. 1) display an enhancement of this post-inhibitory facilitation beyond the maximal recording capacity of the polygraph.

Facilitation (CF) and inhibition (CI) were observed to be rapidly and significantly depressed in eight additional pentobarbital anesthetized high spinal animals given large

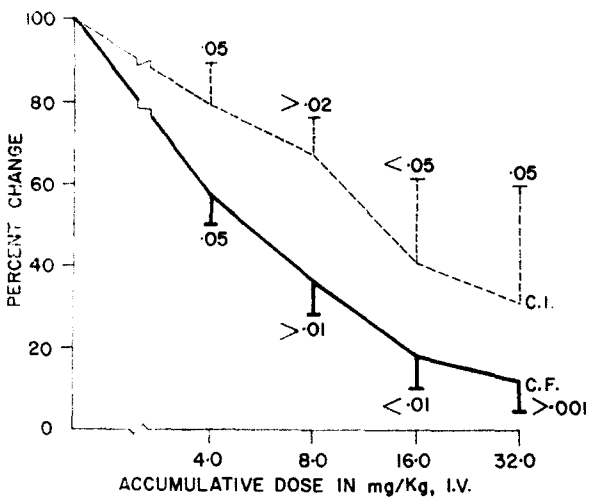


FIG. 3. CF represents the mean percent facilitation of the patellar reflex during a 5-sec period of electrical stimulation of a cervical spinal cord facilitatory area.
CI represents the mean percent inhibition of the patellar reflex during a 5-sec period of electrical stimulation of a cervical cord inhibitory area. A paired comparison student "t" test was used for each dose comparing the observed response to control. The "P" value is indicated above each point. The control period was 15 min and the interval between doses of CPZ was 10 min. The data summarizes the results obtained from eight animals. The short vertical bars drawn in one direction represent ± standard error.

doses of CPZ (4–32 mg/kg) (Fig. 3). Similar results were obtained in three unanesthetized high spinal animals.

Effects of CPZ on EEG, patellar reflex and mean arterial blood pressure in unanesthetized high spinal (C1) animals

A group of six cats were anesthetized with diethyl-ether. CPZ administration (1–16 mg/kg) was initiated 3–4 hr following spinal cord transection and cessation of ether administration. This time period allowed ample recovery from spinal shock (HUDSON and DOMINO, 1963) and also permitted respiratory elimination of ether anesthesia.

Doses of CPZ characteristically increased the amplitude of the EEG discharge recorded bipolarly between the two hemispheres in the areas of the pericruciate motor cortex (Fig. 4). This increase in amplitude sometimes progressed to grand mal seizure patterns following large doses of CPZ (16–32 mg/kg). Such CPZ induced seizures have been reported by others (SCHLICHTHER, *et al.*, 1956; FAZEKAS *et al.*, 1957). The mean arterial blood pressure was significantly elevated at the accumulative doses of 4 and 8 mg/kg ($P<0{\cdot}02$). This blood pressure elevation was paralleled by a significant increase in the patellar reflex at the same dose levels ($P<0{\cdot}05$).

Sites of operative procedure were infiltrated with 2% lidocaine with 0·001% E in order to reduce the mixed background of facilitation and inhibition known to originate from wound areas in the unanesthetized preparation (HENNEMAN *et al.*, 1949).

Large doses of CPZ (4–16 mg/kg) were given to an additional 8 high spinal unanesthetized cats. In such animals the initial dose of 4 mg/kg produced a significant increase in the mean arterial blood pressure ($P<0{\cdot}02$). The patellar reflex was also significantly increased ($P<0{\cdot}05$). Significant alterations in mean arterial blood pressure and patellar reflex were not observed in saline control preparations.

Effects of CPZ on inhibition and facilitation of the patellar reflex produced by stimulation of the sciatic nerve in the unanesthetized high spinal cat

In fourteen high spinal cats facilitation of the patellar reflex was produced by stimulation of the contralateral sciatic nerve at high frequencies (120 c/s) and inhibition was produced by high frequency (120 c/s) stimulation of the ipsilateral sciatic nerve (Fig. 4). Six animals were given accumulative doses of 1–16 mg/kg of CPZ and 8 were given 4–16 mg/kg intravenously. The inhibition produced by sciatic nerve stimulation was never significantly depressed by any dose used. Sciatic evoked facilitation was very resistant to doses of CPZ but was significantly depressed by 4 mg/kg ($P<0{\cdot}05$). Changes in facilitation, however, were difficult to interpret due to the gradual increase in the amplitude of the basal patellar reflex (Fig. 4).

Effects of CPZ on preparations with spinal cord hemisection

Fourteen animals were prepared with a hemisection (C1 or T6) of the spinal cord. Experiments were commenced 3–4 hr or 7 days following hemisection. The patellar reflexes were recorded bilaterally. Accumulative doses of CPZ (1–8 mg/kg) were administered intravenously. Facilitation and inhibition of the patellar reflex were elicited by stimulation of mesencephalic facilitatory (BF) and medullary inhibitory (BI) reticular formation contralateral to the hemisection. Spinal cord facilitatory areas (CF) and

inhibitory areas (CI) ipsilateral and caudal to the hemisection were also stimulated. In addition a reciprocal inhibition of both hindlimb reflexes was periodically observed at time intervals determined by the patellar hammers used. One hammer struck the patellar tendon once per second while the other hammer had a slightly higher frequency. Due to this difference in frequency there were periods of 4–5 sec in which one hammer would strike its patellar tendon and be followed in a few milliseconds by the other patellar hammer. Under these conditions the hammer striking first produced an inhibition of the contralateral patellar reflex. The faster hammer would approach, become synchronous with and then bypass the slower patellar hammer. This gave periods in which each hammer preceded the other by a matter of milliseconds. Such inhibition is depicted in Fig. 5 by black markers above and below the reflex excursions and is referred to as reciprocal inhibition (RI).

Electrical stimulation of BF, BI, CF and CI produced primarily reciprocal effects on the patellar reflexes. However, some non-reciprocal responses were observed from reticular and cord stimulation. These were by far in the minority. Mean arterial blood pressure was usually elevated with the stimulation of BF and decreased with the stimulation of BI as shown in panel A of Fig. 5. However, this response was not consistent. The reverse was observed in some animals.

Doses of CPZ (1–8 mg/kg) produced a differential effect on the two patellar reflexes. One mg/kg of CPZ produced a depression of the patellar reflex contralateral to the hemisection of the spinal cord (Fig. 5, panel B, lower trace). Panels B–E depict a maintained depression of the contralateral patellar reflex (lower trace) and a concomitant increase in the patellar reflex ipsilateral to the hemisection (upper trace) in response to increasing doses of CPZ. This type of response was most frequently encountered. However, on occasion both reflexes exhibited an increase or no change in amplitude as in a preparation with a completely sectioned spinal cord. This latter response may be related to inadvertent trauma to the unsectioned portion of the cord. In a few animals with incomplete hemisections a depression of both reflexes was observed.

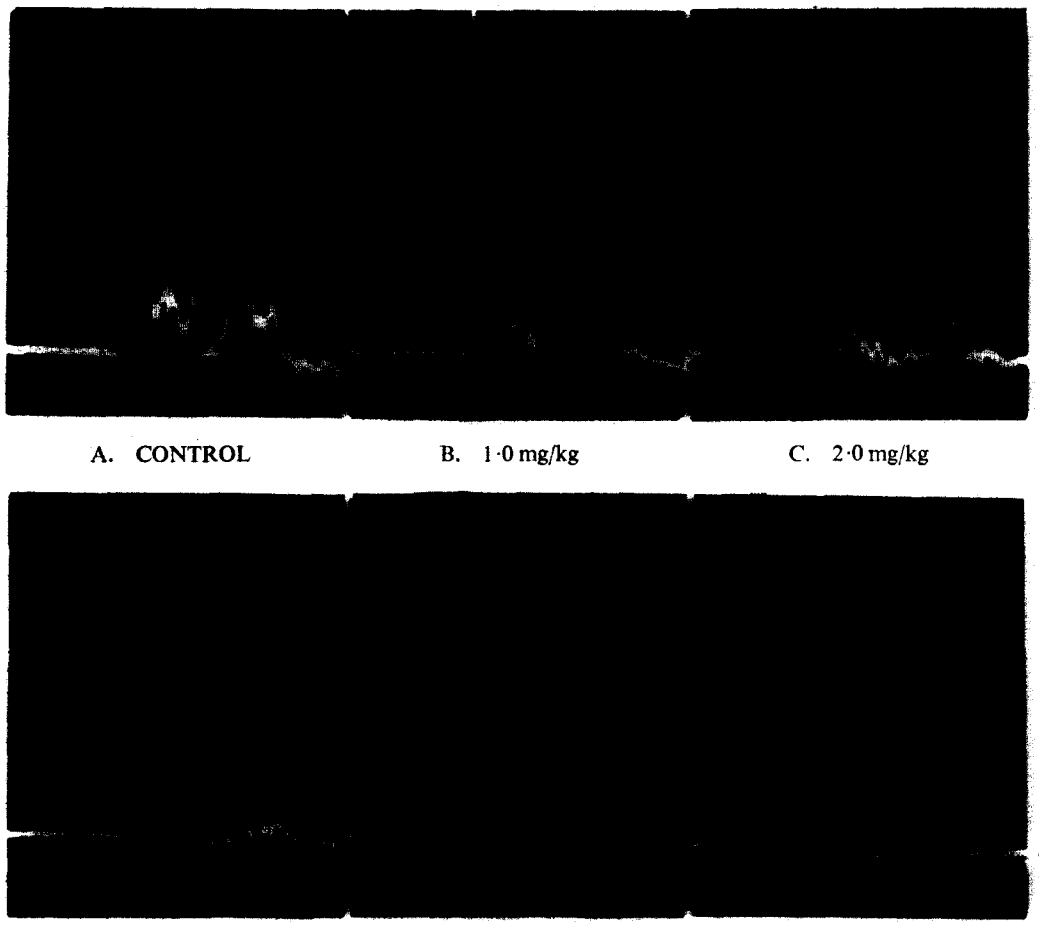
Facilitation and inhibition produced by stimulation of reticular formation and the spinal cord were progressively depressed by doses of CPZ. However, it will be noted in the lower trace of panel B, Fig. 5 that inhibition produced by stimulation of BI is converted to facilitation by 1 mg/kg of CPZ. The reciprocal inhibition (RI) of the patellar reflex contralateral to the section was observed to be lengthened in duration following the dose of 1 mg/kg of CPZ as compared to control. The reciprocal inhibition of the reflex ipsilateral to the section was progressively attenuated as the reflex increased in amplitude (panel B–E, Fig. 5).

In confirmation of MARTIN and EADES (1960) doses of CPZ produced a progressive depression of the blood pressure responses produced by midbrain reticular (BF) stimulation but prolonged the duration of the pressor response. Such an effect can be observed by comparing panel A with panels C, D, and E of Fig. 5. The depressor response to stimulation of medullary reticular formation (BI) was attenuated by doses of CPZ (Fig. 5).

Cats allowed to recover for 7 days following cord hemisection showed similar differential responses of the patellar reflexes to CPZ, the contralateral reflex being depressed while the ipsilateral reflex remained resistant to depression. The level of hemisection produced no significant difference in response.

Effect of CPZ on monosynaptic and polysynaptic segmental potentials in the high spinal (C1) animals

The effects of CPZ on electrically evoked monosynaptic and polysynaptic segmental potentials were studied in 6 spinal laminectomized cats with high spinal cord (C1) transection. These animals had recovered from diethyl-ether anesthesia and were immobilized by D-tubocurarine. Submaximal (80 per cent of maximum) electrical stimulation of the dorsal root produced a large monosynaptic and polysynaptic discharge which was recorded from ventral root L7 (Fig. 6).



A. CONTROL B. 1·0 mg/kg C. 2·0 mg/kg

D. 4·0 mg/kg E. 16·0 mg/kg F. 32·0 mg/kg

FIG. 6. Effects of CPZ on monosynaptic and polysynaptic action potentials of the segmental reflex of a high spinal (C1) cat immobilized with D-tubocurarine. Sub-maximal (80% max.) stimulation of the dorsal root was used. The voltage and time base calibration are indicated.

Panel A — Control B.P. 60.

Panel B — Potentials after 1·0 mg/kg of CPZ given intravenously, B.P. 65.

Panel C — Potentials after 2·0 mg/kg of CPZ given intravenously as an accumulative dose 10 min later. B.P. 66.

Panel D — Potentials after 4·0 mg/kg given intravenously as an accumulative dose another 10 min later. B.P. 69.

Panel E — Potentials after 16 mg/kg given intravenously as an accumulative dose another 10 min later. B.P. 88.

Panel F — Potentials after 32 mg/kg given intravenously as an accumulative dose another 10 min later. B.P. 105.

Panels A–F (Fig. 6) depict the progressive depression of the polysynaptic potentials produced by doses of CPZ (1–32 mg/kg). This depression was statistically significant at all dose levels (Table 1). Rapid injection rates of large doses (e.g. 16–32 mg/kg) produced a fall in the mean arterial blood pressure followed by a decrease in the amplitude of the monosynaptic spike discharge. Such depression of the monosynaptic spike was not observed with slower injection rates. CPZ in accumulative doses of 4–32 mg/kg produced a significant elevation in the mean arterial blood pressure (Table 1). This elevation in mean arterial blood pressure was not paralleled by any significant alteration in the monosynaptic potential.

TABLE 1. EFFECTS OF CPZ ON MEAN ARTERIAL BLOOD PRESSURE, MONOSYNAPTIC AND POLYSYNAPTIC SEGMENTAL POTENTIALS IN HIGH SPINAL (C1) CATS IMMOBILIZED WITH D-TUBOCURARINE ± S.E.

Accumulative dose of CPZ mg/kg, i.v.	Parameters measured	Mean percent of control ± S.E.	*P* Values
Control	M.A.B.P.	100	
	Monosynaptic	100	
	Polysynaptic	100	
1·0	M.A.B.P.	107·8 ± 4·0	>0·1
	Monosynaptic	96·0 ± 3·2	<0·3
	Polysynaptic	79·5 ± 6·1	0·02
2·0	M.A.B.P.	113·0 ± 6·6	<0·1
	Monosynaptic	94·2 ± 3·5	<0·2
	Polysynaptic	72·9 ± 7·3	>0·01
4·0	M.A.B.P.	119·6 ± 8·1	0·05
	Monosynaptic	92·5 ± 3·7	>0·1
	Polysynaptic	61·7 ± 8·7	<0·01
8·0	M.A.B.P.	143·4 ± 16·4	<0·05
	Monosynaptic	92·9 ± 5·1	>0·2
	Polysynaptic	58·7 ± 10·7	>0·01
16·0	M.A.B.P.	143·1 ± 10·7	<0·01
	Monosynaptic	95·3 ± 6·3	<0·5
	Polysynaptic	55·1 ± 11·5	>0·01
32·0	M.A.B.P.	145·4 ± 16·3	0·05
	Monosynaptic	70·8 ± 15·4	>0·1
	Polysynaptic	16·5 ± 10·1	>0·001

The peak height of the monosynaptic and polysynaptic potentials are expressed as per cent of control. Each measurement represents the average of ten consecutive sweeps at each dose level. A paired comparison student "t" test was used for each dose comparing the observed response to control. M.A.B.P. represents the mean arterial blood pressure. Control M.A.B.P. in mm Hg was 83·2.

DISCUSSION

CPZ has been demonstrated to reduce skeletal muscle tone in the experimental animal (DASGUPTA and WERNER, 1955). Impulses originating in the brainstem reticular formation play an important role in the control of the excitatory tonus of lower motoneurons and skeletal muscle tone (MAGOUN and RHINES, 1947; GRANIT, 1955). Available evidence

indicates that the depression of motor function by CPZ is exerted primarily upon the brainstem reticular formation. The present investigation suggests that CPZ also produces a depression of these reticular impulses at a spinal level. Reticulospinal pathways facilitating and inhibiting spinal cord motor activity descend to lumbar segments (VERHAART, 1953) and distribute primarily in the lateral and ventral funiculi of the spinal cord (NIEMER and MAGOUN, 1947). These descending reticular fibers do not make direct connections with lower motoneurons but produce their effects via propriospinal relays and internuncial neuron pools (LLOYD, 1941b).

In high spinal animals, electrical stimulation of descending tracts at cervical cord levels produced facilitation and inhibition of the patellar reflex. These impulses activated at cervical levels which descended to lumbosacral anterior horn cells were reduced by doses of CPZ. The site of CPZ action in this preparation must then be somewhere between the initial cervical segment and the lumbar output to the quadriceps muscle complex.

The resistance of the patellar reflex and the monosynaptic spike potential to depression by CPZ suggest little effect of CPZ directly on lower motoneurons. On the other hand, the significant depression of evoked facilitation and inhibition (Fig. 3), polysynaptically mediated cross extensor reflex and the segmentally evoked polysynaptic discharge (Fig. 6 and Table 1), suggest the internuncial neuron as a possible recipient of the depressant effect of CPZ at a spinal level. Thus the effect appears to be present within pathways descending on lower motoneurons.

The reticular pathways activated are known to influence both α and γ motoneurons (GRANIT, 1955). However, the specific involvement of α and γ motor systems in the mediation of facilitation and inhibition was not determined. Therefore, the depression of facilitation and inhibition could not be attributed to any specific pathway descending upon α or γ motoneurons.

The enhancement and prolongation of the post inhibitory rebound facilitation of the patellar reflex (Fig. 1) offers additional evidence for a spinal cord effect of CPZ. As the inhibition (CI) was progressively depressed the rebound facilitation occurred much earlier, even during the period of stimulation (panel C, Fig. 1). SHERRINGTON (1906) suggested that in cases of rebound facilitation the prior inhibition lowered the threshold for the aftercoming extension reflexes and increased their afterdischarge. After the cessation of inhibition, extensor arcs were considered to be in a phase of exhalted excitability. Inasmuch as the inhibition was progressively depressed while the facilitation was enhanced and occurred with decreased latency, it would appear that inhibition and rebound facilitation are produced by separate terminal pathways. Thus, the increased rebound effect may be an unmasking of a facilitation as a consequence of the depression of the evoked inhibition.

Even though supraspinal tonic effects are removed by cord section, the spinal animal exhibits an increased background of extensor inhibition and flexor facilitation which involves internuncial neurons (VAN HARREVELD, 1940; RUCH and WATTS, 1934; RUCH, 1936; AUSTIN and MCCOUCH, 1954). If CPZ produced a diminution of this background inhibition an increase in the amplitude of the patellar reflex would be expected. Such an elevation of patellar reflex amplitude was observed. However, in most instances, due to much variability, this increase was found to be statistically insignificant.

HERMAN and BARNES (1964) presented evidence for a depressant effect of CPZ on background inhibitory neuronal activity of the spinal cord. Utilizing the Sherrington decerebrate animal these authors were able to produce a Schiff–Sherrington decerebrate prepara-

tion by reversible cold block of the spinal cord at a mid-thoracic level. Small doses of CPZ increased the forelimb rigidity produced by cold block to more than that obtained in the control. The enhancement of a forelimb rigidity in the Schiff-Sherrington decerebrate animal presumably is due to release from a source of inhibition originating below the level of spinal block (RUCH, 1936). This suggests the existence in the intact animal of ascending tracts which, directly or indirectly, exert a continuous restraining or inhibitory action upon the extensor motoneurons of the forelimbs (RUCH and WATTS, 1934). However, since in the Schiff-Sherrington decerebrate animal supraspinal inhibitory and facilitatory systems remain functionally intact with the spinal cord, there is an inherent danger in interpreting the observed response as an effect of CPZ directly on the spinal cord.

Animals with hemisectioned spinal cords emphasized the importance of altered neurologic background activity in the interpretation of the observed effects of CPZ on the patellar reflex. Nervous activity recorded bilaterally below the level of the hemisection display basic differences in patterns of discharge. TEASDALL *et al.* (1958) demonstrated the hyperexcitability of polysynaptic reflex arcs on the hemisectioned side of the spinal cord in the cat. This lowered threshold for polysynaptic discharge became maximal within a few days following hemisection. The ipsilateral monosynaptic discharge was reduced. The monosynaptic and polysynaptic responses on the intact side appeared normal. TEASDALL *et al.* (1958) suggested that possibly some selective change takes place at the interneuronal level on the hemisected side due to removal of normally existing descending inhibitory influences on polysynaptic mechanisms. In any event, the delicate balance of spinal mechanisms is greatly altered caudal and ipsilateral to the hemisection and the action of CPZ appeared to be related to the differential neurologic background. The contralateral reflex, being more nearly normal as far as supraspinal projections are concerned, was depressed similarly to the intact animal while the ipsilateral reflex showed no significant depression.

The reflex on the hemisectioned side was not totally isolated from supraspinal influences as was evidenced by bilateral reflex responses to contralateral brainstem stimulation. This bilateral effect was present in animals with C1 and T6 hemisections. However, since the patellar reflexes were differentially affected by doses of CPZ, the fibers from the brainstem which crossed below T6 probably produced minimal effects on the hemisected side. It is important that this differential effect can be shown in the same animal since CPZ is known to produce different responses in various neurologic preparations. For example, if CPZ is administered to the intact animal it produces a depression of the patellar reflex (BEIN, 1957; SILVESTRINI and MAFFII, 1959; HUDSON and DOMINO, 1964); in the decerebrate preparation it causes an increase in the patellar reflex (DERISIO and MANGHI, 1954) and in the spinal animal it produces no statistically significant alteration of this reflex. The hemisectioned preparation demonstrates the need for supraspinal drive for the manifestation of patellar reflex depression by CPZ. On the other hand, this preparation shows that the brainstem reticular formation is not the exclusive site of CPZ action on lower motor reflexes.

Since motor reflexes evoked by supramaximal stimulation are resistant to CPZ (HUDSON and DOMINO, 1963) one might argue that the differential depression observed in the hemisectioned preparations was due to a large disparity in the intensity of stimulation produced by the patellar hammers. This did not appear to be the case. Animals with the central nervous system intact were given intravenous doses of CPZ while recording the patellar reflex bilaterally. Both reflexes underwent a parallel and significant depression.

In a matter of 6–18 hr STAVRAKY (1961) has been able to show similarly rapid occurring differential responses to chemical agents following unilateral deafferentation of the hindlimb of the cat. Other central nervous system structures such as the cerebral cortex have been observed to become hypersensitive to electrical and chemical stimulation in 4–6 hr as a result of partial isolation (STAVRAKY, 1961). Hypersensitive responses to CPZ in the clinic have also been observed in patients with central nervous system lesions. LOMAS *et al.* (1955) and LIDDELL and RETTERSTOL (1957) showed that CPZ produced epileptic fits almost exclusively in patients who had leucotomies. These seizures were not related to dosage or duration of treatment. Such findings further emphasize the important relationship between the neurologic background and the observed response.

By using the classic dorsal root-ventral root preparation (LLOYD, 1941c) efferent activity could be obtained directly from the spinal cord thus eliminating possible effects of peripheral structures. In such a preparation with high spinal section, doses of CPZ (Table 1 and Fig. 6) produced a significant depression of the polysynaptic discharge. PRESTON (1956) demonstrated similar findings but considered the polysynaptic depression equivocal. The variance between the present study and that of Preston may be attributed to the difference in the preparations used. Preston stimulated the central end of the cut peroneal or gastrocnemius nerves whereas in the present investigation the intradurally isolated dorsal root at L7 was stimulated. Direct stimulation of the dorsal root produces a greater activation of polysynaptic pathways than muscle nerve stimulation. Thus several modalities were subjected to the effects of CPZ.

KRIVOY (1957) and SILVESTRINI and MAFFII (1959) demonstrated that polysynaptic potentials were more susceptible to the depressant effects of hypotension than the monosynaptic potentials. Significant reduction in mean arterial blood pressure was only observed with large doses (32–64 mg/kg) and this was apparently related to the rate of injection. In fact, mean arterial blood pressure tended to increase (Table 1). Therefore, CPZ induced hypotension can be eliminated as a possible causative factor of polysynaptic potential depression in these animals.

The above examples illustrate clear evidence for an internuncial site of action of CPZ at a spinal level. On the other hand, inhibition of the patellar reflex resulting from stimulation of the ipsilateral sciatic nerve was never observed to be significantly depressed (Fig. 4). This mammalian central nervous system inhibitory pathway has for a long time been a subject of controversy. LLOYD (1941a, 1946a, 1946b, 1960) suggested that Ia afferent fibers may produce inhibition of motoneurons monosynaptically. ECCLES (1964) contradicts this conclusion and suggests that inhibition produced by Ia afferents must be mediated via interneurons. It has further been suggested that interneurons are present in the inhibitory pathways to motoneurons from groups II and III afferents (ECCLES and LUNDBERG, 1959). Under these circumstances the simplest inhibitory pathway would be disynaptic. If we accept the argument of ECCLES (1964) we must concur that disynaptic pathways can also exhibit maximal resistance to the depressant effects of CPZ (SII in Fig. 4).

The resistance of some interneurons to depression by CPZ may be indicated in the results obtained by VALDMAN (1962). VALDMAN showed that CPZ depressed facilitation evoked by stimulation of the rostral parts of the pons but did not change the facilitation evoked from the caudal part of the pons. CPZ also depressed inhibition evoked from the vestibular nuclei but had no action on inhibition elicited by stimulation of the dorsal tegmental reticular nuclei. VALDMAN (1962) suggested that these differences in response to CPZ

were due to the properties of morphologic structures of the reticular formation. Such differences in some degree may extend to the spinal cord. KRUGLOV and SINITSYN (1959) produced inhibition by stimulating reticulospinal tracts at cervical cord levels in the decerebrate cat. CPZ did not depress this patellar reflex inhibition. Since monopolar stimulating electrodes were used, it might be argued that current spread was partially responsible for the results observed. However, even with bipolar stimulation 2 of the 18 spinal animals stimulated at cervical cord levels reported here presented evoked inhibition completely resistant to doses of CPZ. Differential histologic localization of resistant and non-resistant areas were equivocal. Such a variance in susceptibility and resistance of bulbospinal polysynaptic systems to chemical agents may indicate (among other things) a difference of spinal neurohumoral transmitters. Cholinergic, serotonergic, adrenergic and other types of neurohumors have been considered (KISSEL and DOMINO, 1959; ESPLIN and ZABLOCKA, 1964; CARLSSON *et al.*, 1964).

The internuncial neuron at spinal levels and the presence or absence (*in toto* or in part) of supraspinal influences appear to be very important to the kind of effects observed on motor systems with doses of CPZ. The specific nature of effects of CPZ on animals with spinal cord and other central nervous system lesions must await further investigation.

The mean arterial blood pressure in general showed a significant elevation following large doses of CPZ (4–8 mg/kg). This occurred in both the anesthetized and the unanesthetized high spinal animal. The observed elevation is therefore not caused by variations in the depth of anesthesia. Such an elevation was never noted in any control preparation. In an earlier study (HUDSON and DOMINO, 1963) mean arterial blood pressure changes in high spinal cats were followed for 6 hr. No significant alterations were observed. This would rule out a gradual recovery from spinal shock as a possible mechanism of the mean arterial blood pressure elevation. In addition, large doses of CPZ produced significant elevation of the mean arterial blood pressure regardless of whether they were given as the accumulative dose or as the initial dose. It is possible that a CPZ effect on the adrenal medulla may be partially responsible for the blood pressure elevation observed. BRUNAUD *et al.* (1953) and MALMEJAC *et al.* (1954) have demonstrated that small doses of CPZ (1 mg/kg) may cause increased secretion of E from the adrenals. This enhanced secretory effect was reported to be blocked by large doses of CPZ (18–20 mg/kg). On the other hand, CPZ has been shown to have α adrenergic blocking properties (HUIDOBRO, 1954; LEAR *et al.*, 1956). Under such a circumstance as increased adrenal secretion one might expect a hypotensive response due to E reversal. However, MARTIN *et al.* (1960) utilizing the spinal vagotomized cat demonstrated that CPZ did not suppress levarterenol-induced vasopressor responses. On the contrary, CPZ enhanced and markedly prolonged the pressor responses to levarterenol. CPZ sulfoxide was shown to prolong the duration of 1-E evoked tachycardia and pressor responses. MARTIN *et al.* (1960) suggested that CPZ may depress some deactivating process of adrenergic amines. Studies in adrenalectomized animals are indicated in order to evaluate the possible relationship of adrenal medulla to the observed blood pressure increases.

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Résumé—Les effets de la chlorpromazine (CPZ) sur reflexe patellaire, et sur les potentiels evoques par stimulation segmentaire furent determines chez le chat en preparation spinale superieure, et en preparation spinale semisectionnee.

L'administration intra-veineuse de chlorpromazine (CPZ) en dose cumulative, n'entraine aucune dépression, statistiquement significative du reflexe patellaire et des potentiels monosynaptiques, évoqués par stimulation segmentaire—le potential polysynaptique évoqué par stimulation segmentaire subit une dépression significative (1–32 mg/kg). Le CPZ s'est révèlé être la cause de la dépression significative de la facilitation et de l'Inhibition du réflexe patellaire produite par stimulation electrique, des cordons latéraux et ventraux de la moelle cervicale (segments 1 et 2). La facilitation du reflexe patellaire, engendrée par stimulation controlaterale du nerf sciatique résista. à des doses de CPZ mais subit une dépression significative à une dose de 4 mg/kg. Il n'a jamais été observé que l'inhibition du réflexe patellaire produite par une stimulation ipsilatérale du nerf sciatique ne fût déprimée par les doses utilisées dans cette étude. Le réflexe patellaire enregistré, ipsilatéral à une semi-section de la moelle cervicale supérieure (C1) et mi-thoracique (T6) resista a des doses de CPZ (1–8 mg/kg) Tandis que le réflexe patellaire contralatéral subit une dépression. La tension arterielle moyenne du sang fut élevée de façon significative par des doses de CPZ (4–32 mg/kg) les résultats indiquent que la neurone intercalée de la moelle est un point probable d'impact de CPZ. Des mecanismes possibles d'élévation de tension arterielle sont discutés.

Zusammenfassung—Die Wirkung von Chlorpromazin (CPZ) auf den Patellarreflex und auf segmentär hervorgerufene Rückenmarkpotentiale wurde in hohen und hemisektionalen Katzenrückenmarkpräparationen untersucht. CPZ in Dosen von 1–32 mg/kg (als Kumulationsdosis) intravenös verabreicht rief keine statistisch bedeutende Veränderung des Patellarreflexes und des segmentär hervorgerufenen monosynaptischen Potentials hervor. Das segmentär hervorgerufene polysynaptische Potential war bedeutend vermindert (1–32 mg/kg). CPZ erwies sich als stark schwellenerhöhend und hemmend im Patellarreflex hervorgerufen durch elektrische Stimulierung der Seiton- und Ventralstränge der Halsmarksegmente 1 und 2. Die Schwellenerniedrigung des Patellarreflexes, hervorgerufen durch anderseitige Stimulierung des nervus ischiaticus, wurde durch CPZ Dosen nicht angesprochen; mit 4 mg/kg wurde sie jedoch beträchtlich verringert. Hemmung des Patellarreflexes, hervorgerufen durch selbseitige Stimulierung des nervus ischiaticus, wurde durch in dieser Untersuchung angewandte Dosen niemals verringert. Der Patellarreflex, selbseitig in einem hohen Hals- (C1) und einem Mittelthorakalhalbschnitt (T 6) des Rückenmarks registriert, wurde von CPZ Dosen (1–8 mg/kg) nicht angesprochen, wärend der anderseitige Patellarreflex verringert wurde. Durchschnittsblutdruck in den Arterien wurde durch CPZ Dosen (4–32 mg/kg) stark gesteigert. Der Befund weist auf das internuntiale Rückenmarkneuron als mögliche Wirkungsstelle des Chlorpromazines hin. Mögliche Blutdrucksteigerungsmechanismen werden behandelt.

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