

EFFECTS OF TRIFLUOPERAZINE ON THE CENTRAL NERVOUS SYSTEM OF THE CAT*

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(Accepted 14 September 1965)

Summary—The effects of accumulative doses of trifluoperazine (0.125–8 mg/kg) on the patellar and linguomandibular reflexes and segmentally evoked monosynaptic and polysynaptic spinal cord potentials were determined in the intact cat preparation. Doses of 1–8 mg/kg of trifluoperazine were necessary to depress these reflexes significantly. Reticular evoked facilitation of the patellar reflex was not depressed significantly until the accumulative dose of trifluoperazine reached 8 mg/kg. On the other hand, reticular evoked inhibition was resistant to all administered doses of trifluoperazine (0.125–8 mg/kg). The rigid condition of the Sherrington (gamma-motor driven) decerebrate animal was depressed by 4 mg/kg and abolished by 8 mg/kg of trifluoperazine. These studies were interpreted to indicate a brainstem site and a possible spinal cord site of motor depressant action of large doses of trifluoperazine.

The EEG discharge of subcortical structures in chronically implanted cats was only minimally depressed by 4–16 mg/kg of trifluoperazine. In addition, hypersynchronous discharge and behavioral responses produced by electrical stimulation of the basolateral amygdala were prolonged following doses of trifluoperazine (4–16 mg/kg).

The mean arterial blood pressure was not significantly reduced unless doses of 4–8 mg/kg of trifluoperazine were administered. Trifluoperazine and chlorpromazine (CPZ) were compared in several experiments and possible mechanisms of action discussed.

INTRODUCTION

TRIFLUOPERAZINE, a phenothiazine derivative with a piperazine side chain, has been demonstrated to be 10 times more potent than chlorpromazine (CPZ) in depressing conditioned avoidance and spontaneous motor activity (TEDESCHI *et al.*, 1958). However, side effects such as hypotension, ataxia, drowsiness, lassitude and prostration which are prevalent with increasing doses of CPZ are minimal or absent with doses of trifluoperazine. On the other hand, trifluoperazine produces a greater incidence of extrapyramidal symptoms such as dystonia, tremors, akathisia, motor restlessness, anxiety and other parkinsonian-like conditions (COLE, 1959; FORRESTER, 1958; FRIEND, 1960; and FREYHAN, 1958; HUDSON and CORNMAN, 1959).

HUDSON and DOMINO (1964) compared the motor depressant effects of thioridazine, chlorpromazine and trifluoperazine on the patellar reflex of the unanesthetized rabbit. In this test these representatives of three major classes of phenothiazines ranked thioridazine > chlorpromazine > trifluoperazine in order of depressant potency. This was exactly the reverse order of these agents in the production of extrapyramidal symptoms in man. The authors expressed the opinion that this reverse order was probably not

*Supported by grant MH-05324 USPHS.

The Smith, Kline and French Laboratories kindly provided the trifluoperazine used in this investigation.

coincidentally related to clinical observations, thus suggesting a possible relationship between the motor depressant property of the phenothiazines and the frequency of occurrence of extrapyramidal symptoms.

Even though the available data indicate minor motor depressant actions of trifluoperazine, little quantitative information is available about the effects of this agent on specific motor reflexes. For this reason, the present study was designed to explore the effects of trifluoperazine on some motor reflex mechanisms of the cat.

METHODS

Experiments with mechanically recorded reflexes

Adult cats of both sexes ranging in weight from 2–4.3 kg were used. Animals were anesthetized with diethyl ether during the surgical operation. After the operation, the animals were anesthetized with alpha-chloralose (60 mg/kg i.v.). All preparations were suspended in a Horsley–Clarke stereotaxic apparatus and the patellar reflex elicited once per sec via a mechanically operated hammer. The isometric reflex contractions were recorded on a Grass polygraph. Body temperature was maintained thermostatically, and carotid arterial blood pressure was recorded in each animal.

Bipolar concentric stimulating electrodes were acutely implanted in the mesencephalic facilitatory (BF) and medullary inhibitory (BI) reticular formation. These electrodes were positioned stereotaxically (for details see HUDSON and DOMINO, 1963). The linguo-mandibular reflex (LMR) was elicited once every 5 sec by an electric shock (2–6 V) applied bipolarly to the tongue. A pulse width of 1 msec was used.

Animals with mid-collicular preoptine transections, performed while they were anesthetized with diethyl ether, were suspended in the above-described apparatus for recording patellar reflex and degrees of muscular rigidity. Two to three hours were allowed for these decerebrate preparations to recover from anesthesia produced by ether.

Experiments with acute spinal laminectomy for recording monosynaptic and polysynaptic spinal cord potentials

Spinal laminectomy was performed in the lumbo-sacral region of the spinal cord for isolation of the dorsal and ventral roots of segment L7 or S1. The animal was anesthetized with diethyl ether. Wounds were infiltrated with lidocaine, the animal immobilized with D-tubocurarine and artificially respired. A mineral oil pool was placed above the exposed spinal cord and maintained at a temperature of 37°–38°C. Two to three hours were allowed for the animal to recover from anesthesia produced by ether. The dorsal root was stimulated with square wave pulses at 80 per cent maximal voltage. A duration of 0.5 msec, a frequency of 2 c/s and a sweep speed of 2 msec/cm were used. Monophasic potentials were recorded by crushing the distal end of the ventral root and placing one pole of the bipolar recording electrode upon this crushed area. Responses were observed oscillographically and recorded via a Grass model C4 camera.

Experiments with chronically implanted subcortical bipolar electrodes

Four pairs of bipolar electrodes with an interpolar distance of approximately 0.5 mm were permanently implanted subcortically in cats using aseptic precautions and pentobarbital anesthetic. Electrodes were made from formex-coated number 32 gauge stainless steel wire. Approximately 15 mm diameter non-insulated balls were placed on the tips of

the electrodes using a modification of the method of RILEY (1949) for welding thermocouples. For additional insulation the wires were coated with Epoxylite and baked in an oven at 70°C for 12–24 hr. A stereotaxic instrument was used to place electrodes in the basolateral amygdala, ventralis lateralis of the thalamus, head of the caudate nucleus and globus pallidus or the mesencephalic reticular formation. A modification of the Sheatz and Galambos tripod plate (Texas Tower) was used to hold an Amphenol plug with nine contacts. The Amphenol carrier assembly was placed in the calvarium in key hole slots which were filled with dental acrylic plastic. Following surgical operation the animal was given 400,000 units of penicillin intramuscularly each day for 5 days or as indicated. Three to four weeks were allowed for recovery. The animal was then placed in a shielded, sound proof cage for EEG recording and observation. Brain areas were stimulated when the animal was awake and relaxed. Drugs were administered intravenously through a chronically implanted silastic catheter inserted into the external jugular vein and passed down to the levels of the auricle. A model 5 Grass polygraph was used for recording EEG. Brain sites were confirmed histologically by the Hess iron deposition technique and subsequent staining.

RESULTS

Effects of trifluoperazine on mean arterial blood pressure, patellar and linguomandibular reflexes of alpha chloralose anesthetized cats

Accumulative doses of trifluoperazine (0.125–8 mg/kg) were administered intravenously to six intact cats anesthetized with alpha chloralose. Doses were calculated as base. The accumulative dose of 1 mg/kg produced a significant depression of the patellar ($P > 0.02$) and linguomandibular ($P > 0.02$) reflexes (Fig. 1). This dose produced a 35 per cent

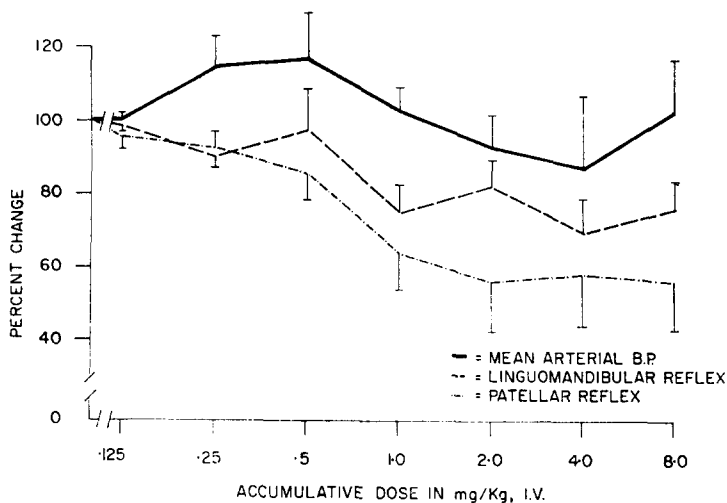


FIG. 1. Effects of trifluoperazine on mean arterial blood pressure, patellar and linguomandibular reflexes in intact cats anesthetized with alpha-chloralose. The patellar and linguomandibular reflexes are expressed as mean percent of control. Each measurement represents an average of five consecutive reflex excursions per dose in each animal. The mean arterial blood pressure was measured in mm Hg and expressed as percent of control. A paired comparison student 't' test was used for each dose comparing the observed response to control. Trifluoperazine was administered at 10-min intervals and accumulative doses were plotted logarithmically. The data summarizes the results obtained from eight animals. The short vertical bars drawn in one direction only represent \pm the standard error.

depression of the patellar reflex (monosynaptic) while reducing the linguomandibular (polysynaptic) reflex only 25 per cent. Panels A and B, (Fig. 2), illustrate the reproducibility of responses obtained during control experiments. Twelve additional cats were prepared and doses of CPZ (0.125–8 mg/kg) were administered. The paired comparison student 't' test showed that the initial dose (0.125 mg/kg) produced a significant depression of the patellar ($P > 0.001$) and linguomandibular ($P > 0.01$) reflexes. The effects of trifluoperazine and CPZ were compared using the group comparison student 't' test. Doses of CPZ (0.125–1 mg/kg) were demonstrated to be significantly more depressant than trifluoperazine. Larger doses of trifluoperazine and CPZ produced a similar depression of the patellar reflex. However, these larger doses of trifluoperazine depressed the linguomandibular reflex significantly less than CPZ. Trifluoperazine produced no statistically significant changes in the blood pressure of the cat anesthetized with chloralose (Fig. 1). CPZ produced a statistically significant depression of mean arterial blood pressure at all dose levels ($P > 0.001$). A group comparison statistical analysis confirmed the greater depressant potency of CPZ on the mean arterial blood pressure.

Effects of trifluoperazine on bulbar-evoked inhibition and facilitation of the patellar reflex

Mesencephalic facilitatory (BF) and medullary inhibitory (BI) areas which are known to exert much control over the excitatory tonus of lower motoneurons (MAGOUN, 1950; GRANIT, 1955) were electrically stimulated via concentric bipolar electrodes. Fig. 2 illustrates the type of responses obtained from such stimulation. In confirmation of KING *et al.* (1955), panel A, Fig. 2, shows the reciprocal responses of the linguomandibular and patellar reflexes evoked by bulbar stimulation. Panel B further demonstrates that the reciprocal effects on the linguomandibular reflex are not due to a current spread to motor nerves of linguomandibular reflex. The stimulation of BI and BF produced no effects on the linguomandibular reflex when it was not being elicited.

Stimulation of BF and BI areas usually produced an increase and a decrease of the patellar reflex amplitude, respectively. BI responses were not significantly altered by any dose of trifluoperazine administered. On the other hand, large doses of trifluoperazine (8 mg/kg) produced a significant depression of reflex facilitation (BF). Control preparations showed no significant changes in reflex facilitation and inhibition in response to physiologic saline solution (Fig. 2).

Effects of trifluoperazine on Sherrington (gamma-driven) decerebrate rigidity

This type of rigidity was very resistant to doses of trifluoperazine (0.125–2 mg/kg). However, the rigid condition was reduced by 4 mg/kg and abolished by 8 mg/kg. Doses of strychnine (50 μ g/kg) caused the return of the rigid state. An additional 8 mg/kg of trifluoperazine produced a transient reduction of the strychnine-induced rigidity. In 5 min or less the rigidity returned, and these animals usually developed sensory precipitous convulsions.

Effects of trifluoperazine on monosynaptic and polysynaptic segmental potentials in the intact cat immobilized with D-tubocurarine

The effects of trifluoperazine on electrophysiologic correlates of monosynaptic and polysynaptic motor reflexes were studied in nine spinal laminectomized animals. Sub-maximal (80 per cent max.) electrical stimulation was applied to the dorsal root (L7 or S1)

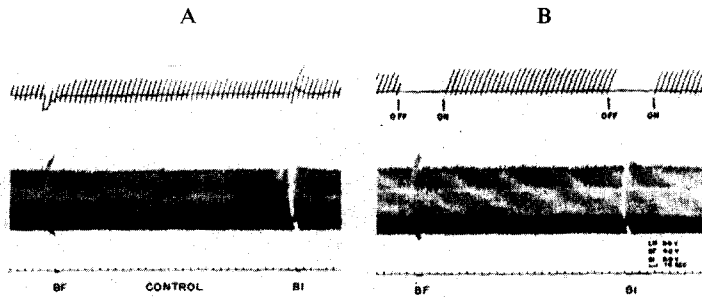
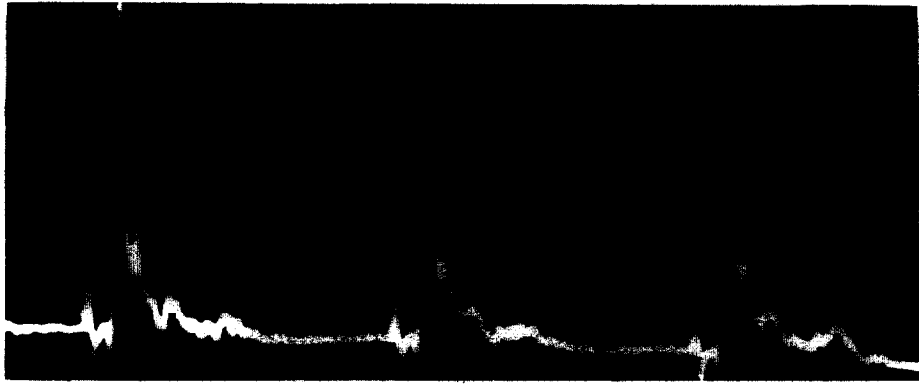


FIG. 2. Panel A. Effects of saline solution on patellar reflex facilitation and inhibition in the cat anesthetized with alpha-chloralose. The patellar reflex was elicited by mechanically tapping the patellar tendon once per sec. B.F. represents a 5-sec period of electrical stimulation of the mesencephalic reticular formation which produces a facilitation of the patellar reflex. B.I. represents a 5-sec period of electrical stimulation of the medullary reticular formation which produces an inhibition of the patellar reflex. The linguomandibular reflex (LMR) contractions shown in the upper trace were elicited by bipolar electrical stimulation to the tongue. Facilitation and inhibition of the LMR is the reciprocal of that of the patellar reflex. Panel B illustrates that this reciprocity of response in the LMR is not due to direct stimulation of LMR pathways at a bulbar level. Note that no mandibular response occurs from reticular stimulation performed in the absence of the elicitation of the LMR.



A Control

B 0.125 mg/kg

C 0.25 mg/kg



D 0.5 mg/kg

E 1.0 mg/kg

F 2.0 mg/kg



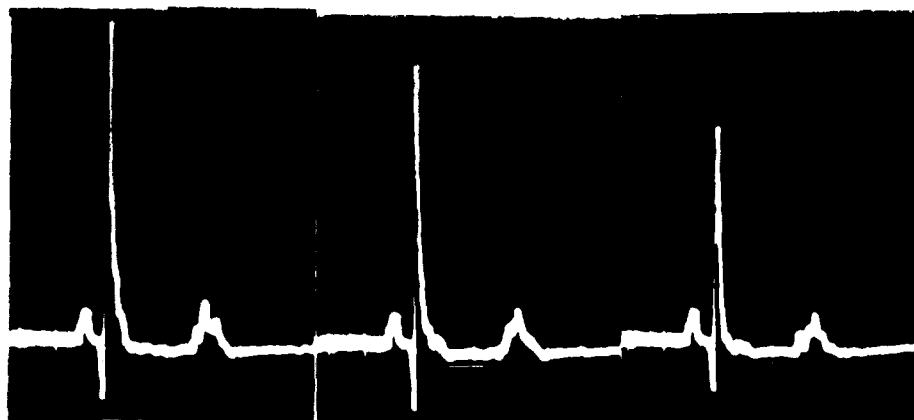
G 4.0 mg/kg

155 μ V
4 M SEC

FIG. 4. Effects of trifluoperazine on monosynaptic and polysynaptic action potentials of the segmental reflex of a cat immobilized with D-tubocurarine.

Sub-maximal (80 per cent max) stimulation of the dorsal root (L7) was used to elicit monosynaptic and polysynaptic electrical discharge recorded at the ventral root (L7). The voltage and time base calibrations are indicated. The initial stimulus artifact is followed by monosynaptic and polysynaptic responses.

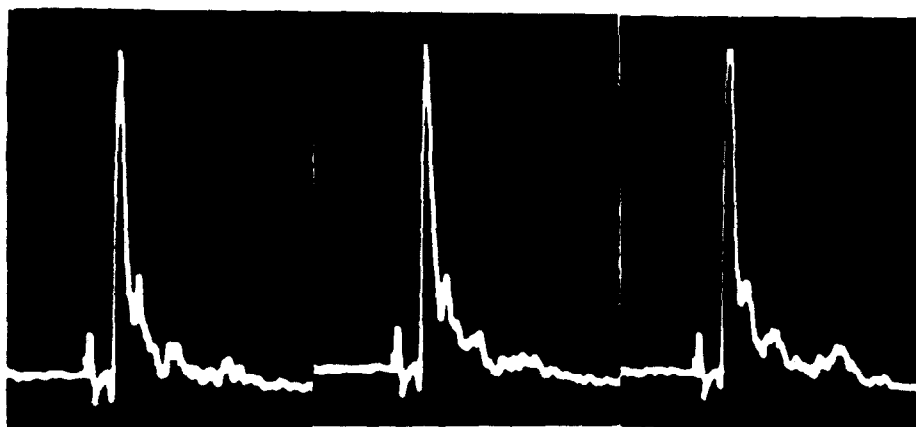
Panel A represents the control response. Panels B-G represent the progressive effects of accumulative doses of trifluoperazine given at 10-min intervals.



A Control

B 0.125

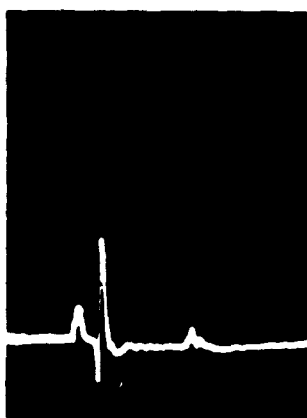
C 0.25



D 0.5

E 1.0

F 2.0



G 4.0

500 UV
4 MSEC

FIG. 5. Effects of CPZ on monosynaptic and polysynaptic action potentials of the segmental reflex of a cat immobilized with D-tubocurarine. The data are expressed in the same manner as in Fig. 4.

of animals recovered from anesthesia produced by diethyl ether, locally anesthetized and immobilized with D-tubocurarine. Fig. 3 graphically depicts the effects of trifluoperazine on monosynaptic and polysynaptic segmental potentials and mean arterial blood pressure.

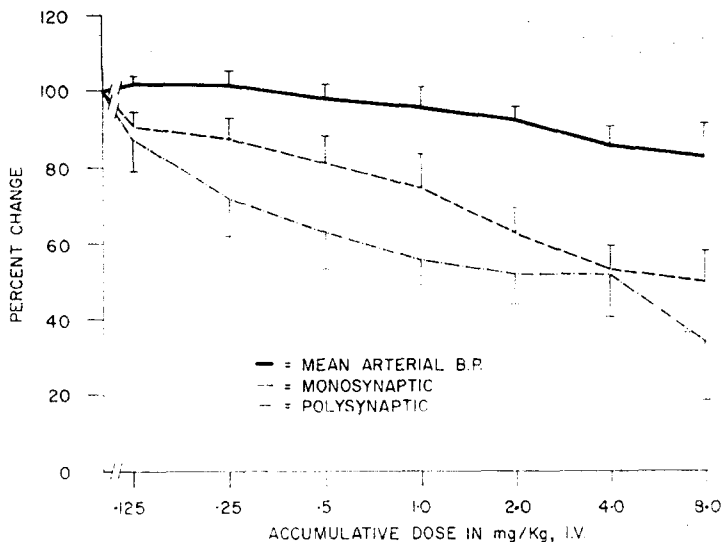


FIG. 3. Effects of trifluoperazine on mean arterial blood pressure and amplitude of the monosynaptic and polysynaptic action potentials of the segmental reflex of cats immobilized with D-tubocurarine. The peak height of the monosynaptic and polysynaptic potentials are expressed as percent of control. Each measurement represents the average of ten consecutive sweeps per animal at each dose level. A paired comparison student 't' test was used for each dose comparing the observed response to control. Data summarizes the results obtained from eight animals. The short vertical bars drawn in one direction only represent \pm the standard error. Control mean arterial blood pressure was 108.2 mm Hg.

Both the monosynaptic and the polysynaptic potentials were significantly depressed by doses of 1–8 mg/kg. Figure 4 illustrates the typical monosynaptic and polysynaptic responses recorded from ventral root L7. Doses of trifluoperazine less than 4 mg/kg did not significantly reduce mean arterial blood pressure (Fig. 3).

Eight additional laminectomized animals were prepared and administered CPZ (0.125–8 mg/kg). These doses produced a significant depression of all parameters measured. A group comparison statistical analysis showed that CPZ (0.125–2 mg/kg) more effectively depressed monosynaptic discharge and mean arterial blood pressure than trifluoperazine in equivalent doses. Figure 5 depicts typical ventral root discharge in response to doses of CPZ (0.125–4 mg/kg). It can be noted by comparing Figs. 4 and 5 that CPZ in the dose of 0.25 mg/kg produced a greater percent depression of the monosynaptic spike than 4 mg/kg of trifluoperazine.

Effects of trifluoperazine on electroencephalogram (EEG) of chronically implanted cats

Trifluoperazine was tested in seven cats with chronically implanted electrodes. Bipolar electrical recordings were made from several subcortical nuclei. Animals were placed in a lighted sound-proof recording chamber equipped with a one-way mirror for observation. Drugs were administered intravenously in an accumulative manner every 20–25 min.

Each animal was allowed to recover from drug effects for 10–14 days before being used again. The initial dose of trifluoperazine (4 mg/kg) caused much excitement in all animals tested. They would claw the floor and wall of the chamber as if attempting to escape. Occasionally they would vocalize. This activity lasted for 0.5–1.5 min and was not repeated upon subsequent doses. Figure 6 illustrates typical EEG responses to doses of trifluoperazine. The control EEG (panel A, Fig. 6) usually consisted of low voltage fast frequency

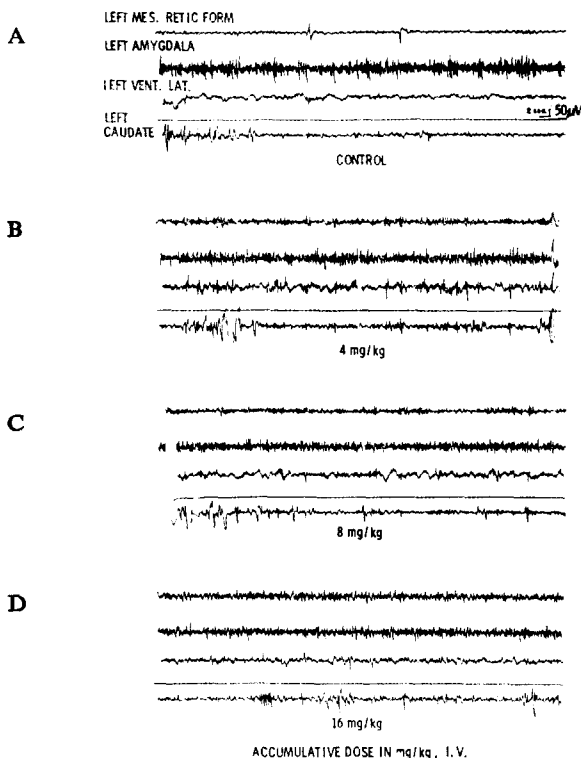


FIG. 6. Effects of trifluoperazine on the EEG of a chronically implanted cat.

Panel A. Control EEG recording of chronically implanted cat.

Panel B. 20 min after 4 mg/kg of trifluoperazine given intravenously via a chronically implanted jugular catheter. Trifluoperazine doses were calculated as base. Note the slight synchronization in reticular formation, ventralis lateralis of the thalamus and the caudate nucleus.

Panel C. 25 min after 8 mg/kg of trifluoperazine calculated as base. Note the reduction of the spike amplitude of the amygdala.

Panel D. 25 min later. (After 16 mg/kg).

Electrical recordings were taken from the following subcortical structures; dorsolateral mesencephalic reticular formation, basolateral amygdala, ventralis lateralis of the thalamus and the head of the caudate nucleus. All recordings were made from the left side of the brain. The time base represents 2 sec. Voltage calibration 50 μ V on all channels. Bipolar recordings were made from all sites.

activity in all leads except amygdala which showed irregular spike-like activity of 4–6 c/s rhythm and 100–200 μ V amplitude. The initial dose of trifluoperazine (Panel B, Fig. 6) produced a slight synchronization of the EEG. The spiked effect, while still present in

the amygdaloid lead, was somewhat reduced in amplitude. This synchronization was only minimally increased by additional doses of trifluoperazine. Behaviorally the animal remained awake and alert. When removed from the recording chamber these animals were not ataxic, but often showed a slight tremor of the hindlimbs. However, cats which received 16 mg/kg of trifluoperazine exhibited a decrease in normal environmental curiosity. At this time the nictitating membrane was relaxed. The pupil size and the light reflex were not significantly altered.

Animals under similar conditions given doses of CPZ showed a greater tendency toward synchronization of the EEG (Fig. 7). Such animals were also indifferent to the environment, obviously depressed, and ataxic when removed from the recording chamber. Sensory stimulation which previously aroused these animals was much less effective.

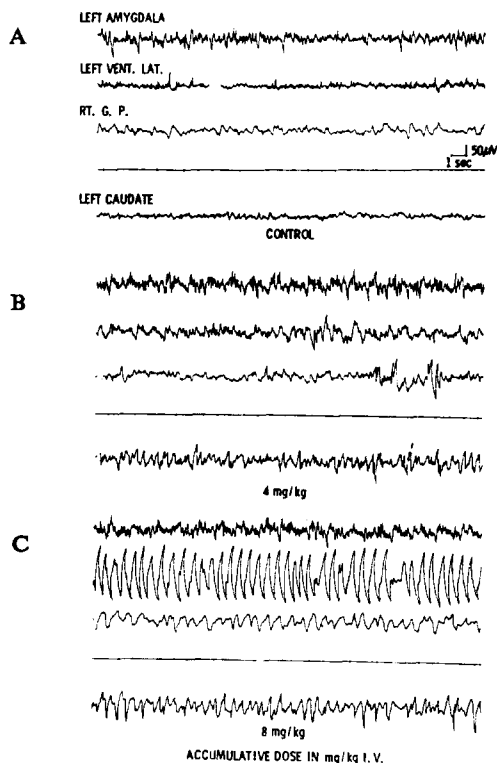


FIG. 7. Effects of CPZ on the EEG of a chronically implanted cat. Panel A. Control EEG recording of a chronically implanted cat. Panel B. 23 min after 4 mg/kg of CPZ given intravenously via a chronically implanted jugular catheter. CPZ doses were calculated as base. Note synchronization of discharge from all leads. Panel C. 20 min after the accumulative dose of 8 mg/kg of CPZ calculated as base. Note large increase in the discharge amplitude of ventralis lateralis of the thalamus. Areas of recording are the same as Fig. 6 except: Rt. G.P.—globus pallidus of the right hemisphere. The time base represents 1 sec. Voltage calibration 50 μ V on all channels. Bipolar recordings were made from all sites.

Effects of trifluoperazine on electrical stimulation of various subcortical structures affecting extrapyramidal motor function

The basolateral amygdala, ventralis lateralis of the thalamus, head of the caudate nucleus, and mesencephalic reticular formation were stimulated bipolarly 4–5 times for a period of 10 sec at 10–15 min intervals during the control period. Effects of trifluoperazine were studied primarily on gross motor function produced by this stimulation. Electrical stimulation of the amygdala at an intensity of 3–5 V, 3 msec duration and a frequency of 40 c/s produced an initial cessation of all motor activity. At a latency of 5–20 sec the classic response of amygdaloid stimulation was observed. Rhythmic ipsilateral facial clonus developed and was associated with chewing, licking, salivation and swallowing movements. Sometimes the animals appeared to be attempting to eject orally something distasteful. Gagging was often associated with this action, but emesis never occurred. The EEG displayed a high voltage, low frequency afterdischarge which spread to other subcortical areas (Panel A, Fig. 8). Attempts were made to avoid stimulus intensities which produced motor seizures. However, stimulation of the amygdala occasionally resulted in a short generalized convulsive motor discharge.

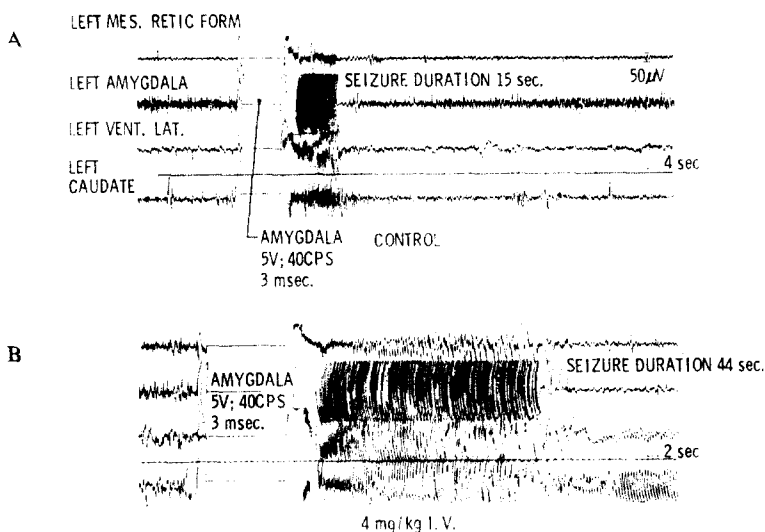


FIG. 8. Effects of electrical stimulation of the basolateral portion of the amygdala and administration of doses of trifluoperazine on EEG discharge. Observations were made in the chronically implanted cat.

Panel A. Depicts control EEG discharge before and after bipolar stimulation of the basolateral amygdala. Note amplitude of after-discharge in the amygdala which spread to other leads. Spike-like activity of amygdala was somewhat reduced immediately following after-discharge but returned rapidly. Stimulus was applied for 10 sec.

Panel B. Forty min after the intravenous administration of 4 mg/kg of trifluoperazine calculated as base. Note the increase in synchrony of discharge before electrical stimulation as compared to the EEG discharge prior to stimulation in Panel A. Bipolar stimulation of basolateral amygdala prolonged the after-discharge in all leads as compared to Panel A. Note difference in time base of Panels A and B. Voltage calibration 50 μ V on all channels. Stimulation parameters indicated. Areas of EEG recording same as Fig. 6.

Nucleus ventralis lateralis of the thalamus was stimulated at 3–5 V, 3 msec duration and a frequency of 8 c/s. This produced flexion of the contralateral limbs, ear tremor, blinking of the ipsilateral eye, turning of the head and the body ipsilaterally. Stimulation of the amygdala during the stimulation of nucleus ventralis lateralis inhibited the ventralis lateralis-evoked motor activity.

The head of the caudate nucleus was stimulated at 4–5 V, 3 msec duration and a frequency of 8 c/s. This caused the animal to crouch as if frightened and turn its head to the contralateral side as if being approached. No seizures were observed with parameters used.

The lateral mesencephalic reticular formation was stimulated at 100 c/s, 1 msec duration and an intensity of 1–2 V. This produced a generalized arousal, both of the EEG and of behavior. Control experiments without trifluoperazine showed that the thresholds remained fairly constant during the period necessary to complete the experiment.

Trifluoperazine apparently increased the excitability of the amygdala. Stimulation of this nucleus following doses of trifluoperazine frequently prolonged the duration of the hypersynchronous EEG discharge and behavioral responses (Panel B, Fig. 8). When such an increase in excitability was observed, it usually proceeded to clonic motor convulsion involving the entire animal. This hypersynchronous electrical activity customarily stopped in amygdala, ventralis lateralis and the reticular formation in a relatively simultaneous manner. However, a high amplitude, low frequency (3–4 c/s) discharge usually continued for 15–50 sec in the caudate nucleus (Panel B, Fig. 8). Prolonged hypersynchronous response to amygdaloid stimulation was most frequently observed after large doses of trifluoperazine (8–16 mg/kg) but occasionally was present after lower doses (Fig. 8).

Motor activity produced by stimulation of other areas in this study was quantitatively depressed by large doses of trifluoperazine (4–16 mg/kg). However, an increase of the intensity of stimulation usually returned the responses toward control levels.

DISCUSSION

It is well known that trifluoperazine produces a very high incidence of extrapyramidal symptoms after both chronic and acute administration (FORRESTER, 1958; COLE, 1959; CAUFFMAN and PAULEY, 1959; CAIN and MALCOLM, 1960; SILVER *et al.*, 1960; VATES and MASUCCI, 1960). On the other hand, trifluoperazine is a very potent agent for reducing conditioned avoidance responses, inducing "catalepsy" and reducing motor activity in animals (TEDESCHI *et al.*, 1958; SHEPHERD and WING, 1962). The observed depression of spontaneous motor activity apparently is not related to any significant dysfunction of the motor apparatus, since noxious stimulation can produce an appropriate, well-coordinated escape response. However, very little quantitative data on the effects of trifluoperazine on specific motor reflexes are available. The present investigation demonstrates that trifluoperazine produces minimal depression on the motor reflex apparatus. In this respect trifluoperazine differs from CPZ. Segmentally evoked monosynaptic and polysynaptic spinal cord potentials, patellar and linguomandibular reflexes and reticular elicited facilitatory and inhibitory modulation of the patellar reflex were all resistant to depression by doses of trifluoperazine. In contrast, the initial dose of CPZ (0.125 mg/kg) produced a statistically significant depression of all parameters tested. A group comparison student 't' test showed that CPZ (0.125–2 mg/kg) was significantly more depressant in all experiments than trifluoperazine. However, large doses (4–8 mg/kg) were usually not significantly different.

In general, the pattern of motor depressant effects of trifluoperazine appeared to be qualitatively similar to that of CPZ. The difference was one of dose. This was further exemplified by the effect of trifluoperazine on Sherrington (gamma motor driven) decerebrate rigidity. The rigid condition was reduced by the accumulative dose of 4 mg/kg and abolished by 8 mg/kg. CPZ completely relaxed this condition at 0.5 mg/kg (HENATSCH and INGVAR, 1956). CPZ has been reported to exert its motor reflex depressant effects primarily at the level of the brainstem reticular formation and spinal cord (DASGUPTA and WERNER, 1955; HUDSON and DOMINO, 1961, 1963; HERMAN and BARNES, 1964; HUDSON, 1964, in press). The present investigation suggests that the same sites are involved in the depressant effects on motor reflex produced by large doses of trifluoperazine. Studies using decerebrate animals showed that areas anterior to a mid-collicular prepontine transection are not necessary for trifluoperazine to produce a motor depressant effect. In addition, large doses of trifluoperazine depressed responses evoked by stimulation of mesencephalic facilitatory reticular formation. The dose differential between CPZ and trifluoperazine with respect to depression of conditioned avoidance and motor reflexes further substantiates the fact that trifluoperazine exerts a more specific central effect than does CPZ. This difference in effects may in some way be related to the differential appearance of extrapyramidal symptoms in response to the two agents. CPZ and trifluoperazine probably produce extrapyramidal symptoms by similar mechanisms. However, manifestation of extrapyramidal symptoms induced by chronic administration of CPZ may be held in abeyance for longer periods of time due to the greater central motor depressant property of this agent. It is well known that in addition to producing pseudo-parkinsonism, as a toxic effect, CPZ has anti-parkinson properties. MANGHI (1954) and BASMAJIAN and SZATMARI (1955a,b) demonstrated that CPZ could reduce Parkinsonian tremor, rigidity and choreic hyperkinesia. Trifluoperazine apparently lacks these anti-parkinsonian properties. The antihistaminic and anticholinergic properties of CPZ may be responsible in some measure for its anti-parkinson effect. BARBEAU (1960) postulated that there is an equilibrium within the central nervous system between two groups of neurohumoral substances: serotonin and the catecholamines on the one hand, and acetylcholine and histamine on the other. Barbeau's evidence indicates that Parkinson's disease is probably a condition of disequilibrium between these substances, inasmuch as the acetylcholine and histamine content of the brain is elevated while the dopamine and serotonin content is decreased. One method by which this condition could be corrected is by the use of antihistaminic and anticholinergic agents. In comparison to trifluoperazine, the antihistaminic and anticholinergic properties of CPZ are relatively strong. With these properties, CPZ may partially control the extrapyramidal condition which it tends to produce. It has been emphasized earlier that phenothiazines such as promethazine, L-mepromazine and CPZ with potent antihistaminic properties are much less likely to produce extrapyramidal reactions than weakly antihistaminic agents such as trifluoperazine and thiooperazine (MCGEER *et al.*, 1961).

The effects of trifluoperazine on EEG discharge further demonstrate some basic differences between trifluoperazine and CPZ. Trifluoperazine in large doses (4-16 mg/kg) produced minimal synchronization of the EEG (Fig. 6). In contrast, slow wave activity was quite apparent in animals given large doses (4-8 mg/kg) of CPZ (Fig. 7). Animals receiving CPZ also presented a classic picture of ataxia, drowsiness, lassitude and prostration. This was not observed in animals receiving similar doses of trifluoperazine.

Signs of trifluoperazine-induced central excitation were observed in response to stimulation of the amygdaloid nucleus (Fig. 8). The afterdischarge produced by electrical stimulation of this nucleus was prolonged following doses of trifluoperazine. KOBAYASHI and HIMWICH (1963) showed a similar increase in excitability of amygdala and hippocampus in the rabbit following chronic administration of doses of trifluoperazine. Other investigators have reported important functional alterations in activity of the amygdala following doses of trifluoperazine and CPZ. Most of these are related to increased excitability and firing rates. ADEY *et al.* (1960) showed that paired amygdaloid-pallidal stimulation decreased single unit firing rates in the midbrain. Following doses of trifluoperazine, the same stimulus facilitated midbrain firing rates. Further amygdaloid stimulation alone produced no effect on midbrain firing rates during control periods, yet after doses of trifluoperazine low frequency stimulation of the amygdala produced bursts of high discharge rates. ADEY and DUNLOP (1960) further demonstrated that CPZ (2 mg/kg) enhanced rhythmic firing rates of reticular neurons in response to paired repetitive stimulation of globus pallidus or amygdala and sciatic nerve. Large doses of CPZ (20 mg/kg) were shown by PRESTON (1956) to produce isolated spikes in the amygdala while 35–40 mg/kg produced seizure discharges. Seizures in response to both CPZ and trifluoperazine have been observed in the clinic (FAZEKAS *et al.*, 1957; CAUFFMAN and PAULEY, 1959). It is not known if these seizures are related to any initial effect on the amygdala or other rhinencephalic structures. It is known that some kind of reciprocal influence exists between the amygdala and the brainstem. BRADLEY (1963) suggests that this influence is probably inhibitory. Thus, interference with this reciprocal relationship could result in a "release" effect and account for the increased activity of the amygdala following administration of some phenothiazines.

There is much evidence which suggests a role for the amygdala in the integration of emotional behavior. However, the evidence with respect to the nature of the effect produced by the amygdala is contradictory and confusing. SPEIGEL *et al.* (1940) and BARD and MOUNTCASTLE (1948) found that bilateral amygdectomy in cats produced a marked increase in savage behavior whereas KLÜVER and BUCY (1939) and SCHREINER and KLING (1953) reported a taming effect of amygdaloid lesions. BARD and MOUNTCASTLE (1948) suggested that the amygdala acts as a funnel through which inhibitory influences originating in the transitional cortex of the midline, in the neocortex and in the amygdala itself exert a suppressing action on the brainstem mechanism. Due to the reported widespread inhibitory influence of the amygdala, PRESTON (1956) suggested that the increased amygdaloid activity produced by CPZ may be involved in its tranquilizing effect. This theory also may be considered as a possible partial explanation of trifluoperazine's tranquilizing property. However, GLOOR (1960) points out that the amygdala does not merely act in an inhibitory manner but rather in a modulatory way on complex somatic, autonomic and behavioral mechanisms integrated in sub-cortical structures. As a modulator the amygdala is able to influence one and the same function in opposite ways. On the other hand, a preferential drug activation of inhibitory function is conceivable. KILLAM and KILLAM (1958) demonstrated that CPZ enhances the inhibitory effect of stimulation of reticular formation on responses in the auditory system.

Résumé—Chez le chat intact, l'effet de doses cumulatives, 0.125–8 mg/kg, de trifluopérazine a été étudié sur les réflexes patellaire et linguomandibulaire ainsi que sur les potentiels mono- et post-synaptiques, évoqués par stimulation segmentaire de la moëlle.

Une dépression significative de ces réflexes a pu être obtenue avec des doses de 1–8 mg/kg. La facilitation du réflexe patellaire induite par stimulation réticulaire n'est déprimée

significativement qu'avec la dose élevée de 8 mg/kg. D'autre part, l'inhibition entraînée par stimulation réticulaire s'est montrée résistante à toutes les doses administrées (0.125-8 mg/kg) de trifluopérazine.

La rigidité de décérébration de Sherrington (système moteur gamma) est diminuée par la dose de 4 mg/kg et abolie par celle de 8 mg/kg.

Ces données sont interprétées dans le sens d'un point d'impact de la trifluopérazine au niveau du tronc cérébral et d'une éventuelle dépression motrice des fortes doses au niveau de la moëlle.

Chez le chat porteur d'électrodes à demeure, la décharge EEG des structures sous-corticales n'est faiblement déprimée qu'après des doses 4-16 mg/kg de trifluopérazine. De plus, les décharges hypersynchronisées et les réactions comportementales, induites par électro-stimulation de l'amygdale basolatérale, sont prolongées par des doses croissantes de 4 à 16 mg/kg.

La baisse de la tension artérielle moyenne ne devient significative que pour une posologie de 4-8 mg/kg.

Une comparaison entre la trifluopérazine et la chlorpromazine (CPZ) est effectuée pour les différentes études et les éventuels mécanismes d'action sont discutés.

Zusammenfassung—Es wurden die Einflüsse von anhäufenden Dosen von Trifluoperazine (0.125-8 mg/Kg) auf die Patellar- und Linguomandibularreflexe, sowie auf segmentär hervorgerufene monosynaptische und polysynaptische Rückenmarkspotentiale im intakten Katzenpräparat bestimmt. Eine Minimaldosis von 1 mg/kg Trifluoperazine war zur bedeutungsvollen Unterdrückung dieser Reflexe notwendig. Reticulär hervorgerufene Förderung des Patellarreflexes wurde erst bei einer anhäufenden Dosis von 8 mg/kg Trifluoperazin bedeutend herabgesetzt. Dagegen war eine reticular verursachte Hemmung gegen sämtliche Trifluoperazindosen (0.125-8 mg/kg) resistent. Der rigide Zustand des nach Sherrington enthirnten (von Gamma-motorischen Nervenfasern getriebenen) Tieres wurde durch 4 mg/kg vermindert und durch 8 mg Trifluoperazin/kg zunichte gemacht. Diese Untersuchungen wurden in dem Sinne interpretiert, dass die motorisch-depressive Wirkung von grossen Trifluoperazindosen ihren Sitz im Hirnstamm und möglicherweise im Rückenmark hat. Die elektroencephalographische Entladung von subcortikalen Strukturen in chronisch implantierten Katzen wurde nur in geringem Masse durch 4-16 mg Trifluoperazin erniedrigt. Ausserdem trat eine Verlängerung der hypersynchronen Entladungen sowie der Verhaltensreaktionen durch elektrische Stimulierungen der basilateralen Mandeln ausgelöst, nach Dosen von Trifluoperazin (4-16 mg/kg) auf.

Der durchschnittliche arterielle Blutdruck zeigte keine bedeutende Senkung, es sei denn dass 4-8 mg Trifluoperazin verabreicht wurden. Es wurden Trifluoperazin und Chlorpromazin (CPZ) in verschiedenen Versuchen miteinander verglichen und mögliche Wirkungsweisen besprochen.

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