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Neurological and Behavioral Toxicity of Kryptopyrrole in the Rat[1,2]

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WALKER, J. L. *Neurological and behavioral toxicity of kryptopyrrole in the rat.* PHARMAC. BIOCHEM. BEHAV. 3(2) 243–250, 1975. – Ten rats were given 9.1 to 82 mg/kg of 2,4-dimethly-3-ethylpyrrole (kryptopyrrole) and the behavioral and electroencephalographic effects were studied. Kryptopyrrole was found to decrease EEG voltage, disrupt synchronization and induce abnormal spiking at a variety of cortical and subcortical sites. Intermittent periods of low frequency hypersynchronous EEG activity were consistently elicited by kryptopyrrole. These waves bear a resemblance to the hypersynchronous EEG patterns associated with hallucinatory agents such as LSD-25. Marked behavioral alterations were observed following the initial injection including ataxia, hyperventilation, locomotor depression and catelepsy. Kryptopyrrole causes major central nervous system dysfunction, and these findings are discussed in the context of a drug-induced model of psychoses.

2,4-Dimethyl-3-ethylpyrrole Kryptopyrrole Mauve factor Electroencephalography Psychoses Psychopharmacology

CHROMATOGRAPHIC monitoring of human urine has identified an Ehrlich-positive spot isographic in the urine of psychiatric patients which because of its Ehrlich reaction has been called mauve factor [7]. Using autotransfer chromatography, Irvine *et al.* [10] demonstrated that a mauve factor negative urine specimen was mauve factor positive when 2,4-dimethyl-3-ethylpyrrole (kryptopyrrole) was added to the specimen. Autotransfer chromatography of aqueous kryptopyrrole was also found by this laboratory to yield all of the components of the usual mauve factor pattern. This work appears to be the first demonstration of kryptopyrrole in the human body.

Mauve factor or kryptopyrrole has been shown to have a statistical association with psychiatric disorders, particularly psychoses. Hoffer and Osmond [6] report that 68% of acute schizophrenics exhibit a positive mauve factor in their urine, while approximately 1/3 of the patients diagnostically classified as neurotic, alcoholic, or mentally retarded showed positive mauve factor. Other laboratories have substantiated the association between mauve factor and human psychiatric conditions [13,15]. O'Reilly *et al.* [13] have found that approximately 11% of nonpsychiatric patients also show a positive mauve factor in their urine. Several studies have excluded the usual sources of preformed pyrroles such as phenothiazines, tobacco and diet as contributory sources in the psychiatric samples [3, 4, 8]. In studies of the intensity of the mauve factor reaction in psychiatric patients, Sohler *et al.* [16] report that in mauve factor positive subjects the daily urinary excretion of kryptopyrrole is approximately 0.2 to 1 mg per 24 hr. The clinical correlates of mauve factor include perceptual disorders, disorientation, signs of organicity, abnormal EEG, various personality traits and poorer therapeutic prognosis [6, 8, 9].

The limited literature on the behavioral effects of kryptopyrrole suggests that the compound has a depressant effect on the CNS and behavior when injected into the mammalian body [11, 13, 16]. Irvine and Zdanivsky [11,12] report that in the rat, kryptopyrrole reduces exploratory behavior in an open field test and also reduces activity in a standard activity wheel. The dosages of kryptopyrrole used by these authors apparently did not interfere significantly with the performance of an overlearned maze task. Performance on a standard operant task appears to be significantly disrupted by kryptopyrrole [11,12]. Animals trained on a FR-30 schedule and then

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[2] Preliminary results of this study were presented at the third Annual Meeting of the Society for Neuroscience, San Diego, 1973.

[3] All animals were treated in accordance with the standards of the Canadian Council on Animal Care.

given kryptopyrrole showed a disruption of operant behavior in which the animals were unable to maintain the previously high rate of responding and consequently received fewer reinforcements. The animals also exhibited a progressive dose-dependent increase in post-reinforcement pauses. Baseline operant performances could apparently be re-established within 24 hr. Kryptopyrrole was also found to inhibit the acquisition of fixed-ratio operant schedules [11,12].

The purpose of the present experiments was to determine: (1) the acute effect of kryptopyrrole injections on the rat EEG recorded from depth electrodes; (2) the effect of chronic administration of kryptopyrrole on the rat EEG; (3) the acute and chronic behavioral correlates of kryptopyrrole.

METHOD

Animals and Surgery

Standard stereotaxic technique was used to chronically implant electrodes in the brains of ten hooded rats. The rats were obtained from the Brandon University breeding colony and were housed singly in standard laboratory cages. They were maintained under a 12 hr dark–illumination cycle throughout the study. The animals weighed between 311 and 465 g at implantation. Sodium pentobarbital (Nembutal) was administered prior to surgery (42 mg/kg). Monopolar macroelectrodes were constructed from Size 00 stainless steel insect pins insulated with epoxylite. Electrode tips were bared for a distance of 0.1 to 0.3 mm. Each rat had 3 chronic electrodes placed according to the atlas of Pellegrino and Cushman [14] using Bregma as reference. Table 1 summarizes the location of the recording sites and the electrode arrays for each rat. After the surface of the cranium was exposed, 2 pairs of holes were drilled from the dorsal to the lateral surfaces of the skull. The holes were placed approximately 1.5 mm anterior to Bregma and 1.75 mm posterior to Lambda. A single strand of stainless steel suture wire was threaded through these holes and twisted together near the midline. This wire served as the indifferent electrode and as an anchor for the electrode assembly [2]. Implantation procedures have been described in detail elsewhere [17].

TABLE 1

ELECTRODE ARRAYS AND ANATOMICAL RECORDING SITES IN EACH ANIMAL

Rat Number	Recording Sites		
20	C	dHpc	RF
22	CSC	LS	VMH
19	C	dHpc	RF
123	AHA	AME	NPT
13	dHpc	RF	MFB
24	CSC	LS	VMH
8	C	dHpc	RF
101	LS	CPU	GL
122	AME	LHA	TCS
99	CPU	GL	CI

C, Cortex; dHpc, Dorsal Hippocampus; RF, Mesencephalic Reticular Formation; CSC, Superior Colliculus; AHA, Anterior Hypothalamic Area; AME, Medial Amygdaloid Nucleus; NPT, Posterior Thalamic Nucleus; MFB, Medial Forebrain Bundle; LS, Lateral Septal Nucleus; CPU, Caudate Nucleus; GL, Lateral Geniculate Body; LHA, Lateral Hypothalamic Area; TCS, Corticospinal Tract; CI, Internal Capsul.

Procedure

A minimum of 2 weeks was allowed between the completion of implantation surgery and the first electrophysiological recordings. Animals were housed in a small Plexiglas chamber and connected to a flexible cable which allowed free movement within the test chamber. Recording instrumentation was located in an adjoining room. A Grass model 79C Polygraph was used for EEG recording, with one-half amplitude low and high attenuation set at 0.3 and 35 Hz respectively. During EEG recording, the behavioral response of the animal was continuously monitored using a closed-circuit television system. The television system did not introduce noise into the EEG records. Behavioral reactions were written on the EEG record.

Prior to the first recording session each animal was placed in the recording chamber for 3 hr on 2 consecutive days with the head plug attached to allow behavioral habituation to the cable and chamber. EEG records were collected during the illuminated phase of the 12 hr dark–light cycle. Consecutive daily recordings were made at the same time for each rat but recording times differ between animals. Purissimum grade aqueous kryptopyrrole was administered intraperitoneally using a Hamilton microliter syringe. Doses of 10 to 90 μl/kg of purissimum grade kryptopyrrole were used. Previous studies of kryptopyrrole injected into the mammalian body have reported drug dose on a μl/kg basis [11,12]. In order to preserve continuity between this study and existing data, a similar procedure was used in this research. The specific gravity of kryptopyrrole is $0.913^{20}{}_{4}$ gm/cc [18]. Making the appropriate μl/kg to mg/kg conversions, the drug doses used in the study range from 9.1 mg/kg (10 μl/kg) to 82 mg/kg (90 μl/kg).

Animals were food deprived for approximately 12 hr prior to all EEG recordings. On the day before the first kryptopyrrole injection a predrug sample EEG was obtained for each rat. Predrug EEG recordings for each rat were collected for a total of 3 hr with 90 sec EEG samples at 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 min following placement in the test chamber. Predrug recordings exhibited normal patterns of spontaneous sleep. Animals received their first kryptopyrrole injection on the day following collection of predrug records. Immediately following injection the rat was placed in the chamber for a total of 3 hr with 90 sec EEG samples collected at 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 min following injection.

Table 2 presents a summary of the experimental treatments and recording schedule used for each animal. The initial injection of kryptopyrrole ranged from 10 to 30 μl/kg. The initial dose level was continued on consecutive days up to a maximum of 8 consecutive sessions. Six of the 10 animals received incremental doses on subsequent

TABLE 2

EXPERIMENTAL TREATMENT SCHEDULE, KRYPTOPYRROLE DOSAGE LEVELS, INJECTION FREQUENCIES AND POST INJECTION FOLLOWUP RECORD

Rat	Baseline	Kryptopyrrole dosage: μl/kg	Increased dosage: μl/kg	Post Injection Followup
20	X	10 (3)*	–	–
22	X	15 (1)	20 (1)†	
			25 (1)	
			30 (4)	
			40 (5)	X
19	X	15 (2)	18 (1)	
			20 (1)	
			25 (1)	
			30 (1)	
			35 (1)	
			45 (1)	X
123	X	15 (2)	30 (1)	
			40 (1)	–
13	X	15 (3)	20 (1)	
			25 (1)	
			30 (1)	
			35 (1)	
			40 (1)	
			50 (1)	
			70 (1)	
			90 (1)	X
24	X	15 (8)	20 (1)	
			25 (2)	X
8	X	20 (2)	–	–
101	X	20 (3)	25 (2)	X
122	X	20 (6)	–	–
99	X	30 (4)	–	–

*Numbers in parentheses indicate the number of consecutive daily EEG recordings made with the initial dosage level.

†Number in parentheses indicate the number of consecutive daily EEG recordings made under the increased kryptopyrrole level.

recording days as indicated in Table 2. Post experimental no-drug EEG recordings were completed on 5 of the animals. The EEG records were analyzed by visual inspection of the tracings because of the lack of computer instrumentation.

Following completion of the experiment the animals were killed with an overdose of sodium pentobarbital and perfused with physiological saline and a saturated solution of potassium ferrocyanide in 40% formaldehyde. A direct current was then passed through each electrode tip. After the brains were removed from the skulls they were blocked, dehydrated, and embedded in paraffin for histological verification of electrode locations.

RESULTS

EEG Voltage

Eight of the 10 rats studied showed consistent voltage decreases in the EEG after recieving the initial injection of kryptopyrrole. The smallest dosage (10 μl/kg) produced the voltage decrement. The 2 rats which did not show any apparent drug-induced voltage decrement had received 15 μl/kg and 20 μl/kg of kryptopyrrole and had electrodes placed in the cortex, dorsal hippocampus, reticular formation, and lateral septal nucleus, ventromedial hypothalamus, superior colliculus, respectively. Of the rats showing voltage decrements on the first injection day, one received 10 μl/kg, 4 animals received 15 μl/kg, 2 received 20 μl/kg and one animal received an initial injection of 30 μl/kg of kryptopyrrole. Examples of no-drug baseline EEG tracings and kryptopyrrole-induced voltage decreases are presented in Fig. 1. The voltage decrease observed in the 8 animals appeared from 15 to 30 min following the initial injection. In all cases where a voltage decrease was observed, it occurred in all 3 electrodes in the array. The EEG voltage decrease persisted in the 8 animals until approximately 120 min after injection at which time the voltage levels returned to baseline levels in all of the animals. Inspection of the EEG tracings did not suggest any relationship between dosage and amount of voltage reduction.

Nine of the animals were studied on subsequent days repeating the initial dosage level of kryptopyrrole. As indicated in Table 2 the number of consecutive daily EEG recordings made with the initial dosage level ranged from 2 to 8 consecutive sessions. A clear tolerance effect was apparent in these data. At all dosage levels there was a tendency for the EEG voltage to return to baseline levels on subsequent recording days under readministration of the initial kryptopyrrole dosage. By the third daily recording session the animals receiving from 10 to 20 μl/kg had EEG voltage levels similar to baseline levels. Rat 122, for example, received 6 daily injections of 20 μl/kg, and on Days 3 through 6 the voltage levels appeared identical to baseline recordings. Rat 30 received 30 μl/kg kryptopyrrole on 4 consecutive recording days and showed reduced EEG amplitude on each of the recording sessions over baseline levels. Fig. 2 presents examples of voltage levels observed in these chronic studies.

Six of the animals in the study received incremental dosages of kryptopyrrole after voltage tolerance effects were established. Increasing the dosage level consistently reduced the voltage of the EEG over the prior recording day. At all of the dosage levels investigated, the EEG voltage returned to baseline levels after several consecutive days of recording at that drug level. Five of the animals received a postinjection followup recording session 24 hr and also 1 week after the last administration of kryptopyrrole. In all cases the EEG voltage levels were not distinguishable from baseline records.

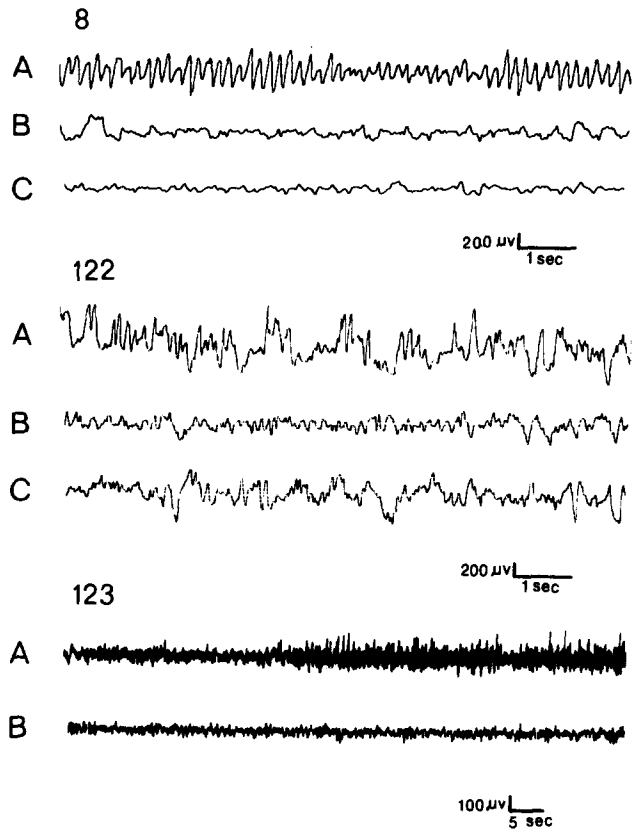

FIG. 1. No-drug baseline EEG tracings and kryptopyrrole-induced voltage decreases. Rat 8: A, dorsal hippocampus, no-drug, 30 min following introduction into chamber; B, dorsal hippocampus, 30 min following 20 μl/kg kryptopyrrole; C, dorsal hippocampus, 30 min following 20 μl/kg kryptopyrrole on the second drug day. Rat 122: A, lateral amygdaloid, no-drug 30 min following introduction into chamber; B, lateral amygdaloid area, 30 min following 20 μl/kg; C, lateral amygdaloid area, 30 min following 20 μl/kg on the second drug day. Rat 123: A, anterior hypothalamic area, no-drug baseline 90 min following introduction into chamber; B, anterior hypothalamic area 90 min following 15 μl/kg.

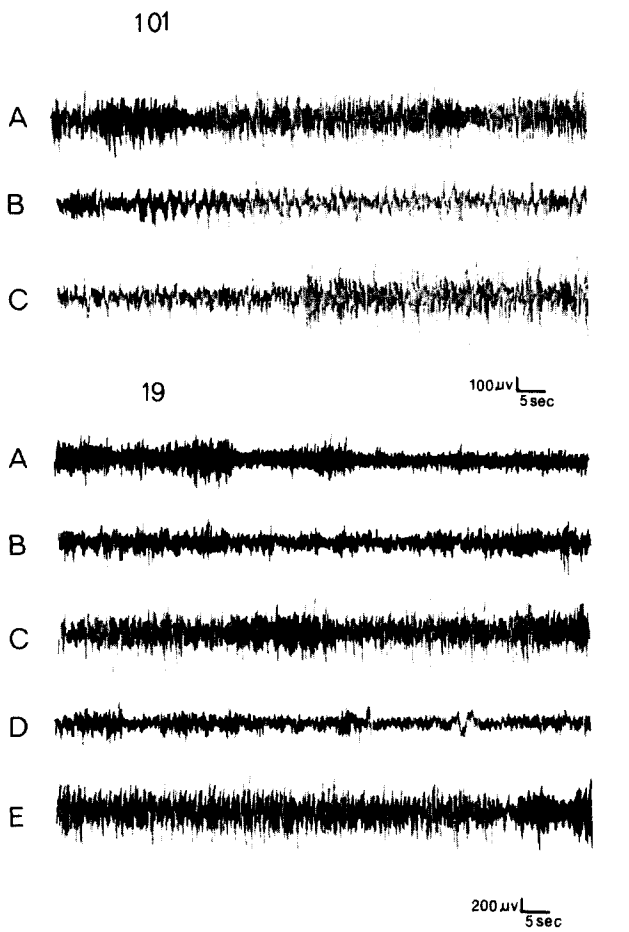

FIG. 2. Voltage levels following chronic administration of kryptopyrrole. Rat 101: A, lateral septal nucleus, no-drug baseline 30 min after introduction into chamber; B, lateral septal nucleus 30 min after 20 μl/kg; C, lateral septal nucleus, 30 min after 20 μl/kg on the second drug day. Rat 19: A, cortex 45 min after 15 μl/kg; B, cortex, 45 min after 15 μl/kg on second drug day; C, cortex, 45 min after 15 μl/kg on third drug day; D, cortex, 45 min after 20 μl/kg on the fourth drug day; E, cortex, 45 min after introduction into the chamber, no-injection, 24 hr after last injection.

High Voltage Hypersynchronous Activity

Kryptopyrrole at all dosages was observed to disrupt synchronized EEG activity at all of the recording sites. Few occurrences of hippocampal theta were observed after administration of kryptopyrrole.

Although kryptopyrrole disrupted synchronized ongoing EEG patterns, irregularity occurring bursts of very high voltage hypersynchronous EEG activity were consistently observed after kryptopyrrole injection. Similar patterns were never observed in the no-drug baseline recordings. Seven of the 10 rats exhibited this EEG pattern during the first recording session following kryptopyrrole administration. All of the rats in the study exhibited these periods of high voltage hypersynchronization following drug administration at some point in the study. Figure 3 shows examples of this EEG pattern. The earliest appearance of this pattern occurred 30 min following injection of kryptopyrrole. When such activity was present it occurred at irregular intervals throughout the three hour recording session. Although the hypersynchronous activity resembled sleep spindles, observation of the television monitor indicated that the eyes of the animal were usually open during such EEG activity and frequently the rats were moving about the test chamber during or immediately prior to the appearance of hypersynchronized activity. The frequency range of this activity was found to be from 6 to 12 Hz.

The occurrence of the high voltage hypersynchronous EEG activity did not appear to be dose-dependent. Rat 13, for example, although exhibiting bursts of hypersynchronous activity during the first 2 recording sessions (15 μl/kg), did not show additional bursting at subsequent dosages as high as 90 μl/kg. Evidence of acquired tolerance to the bursting effect was observed. No evidence of high voltage hypersynchronous was observed when the initial dosage level of kryptopyrrole was continued beyond four subsequent recording days. Three rats (Animals 24, 122 and 99) met this criterion, and none of these animals exhibited

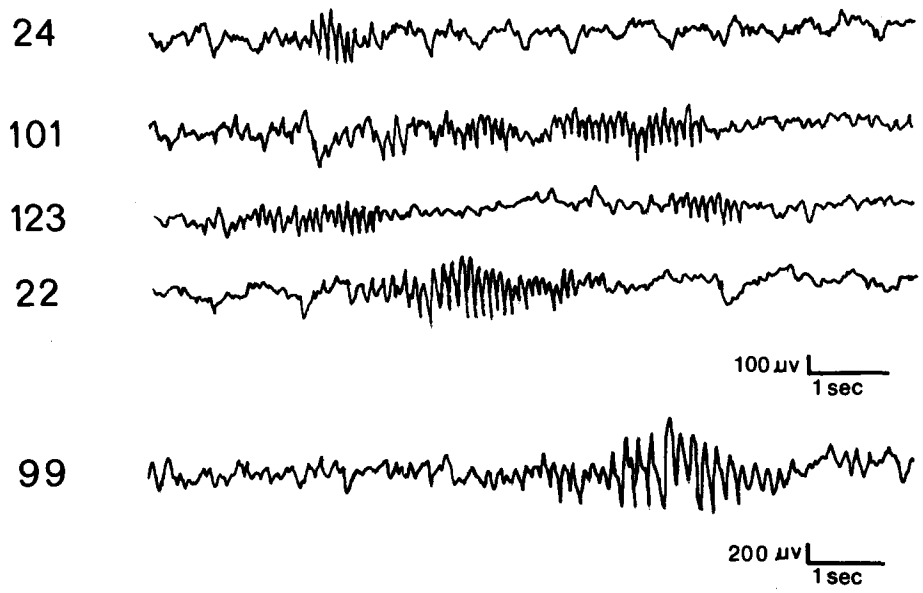

FIG. 3. Kryptopyrrole-induced bursts of high voltage hypersynchronization. Rat 24: lateral septal nucleus, 10 min following 15 μl/kg on the second drug day. Rat 101: lateral geniculate body, 15 min following 20 μl/kg on first drug day. Rat 123: medial amygdaloid area, 90 min following 30 μl/kg on the third drug day. Rat 22: ventromedial hypothalamic nucleus, 165 min following 25 μl/kg. Rat 99: lateral geniculate body, 75 min following 30 μl/kg.

bursts of hypersynchronization on day four or subsequent days under the initial dosage level. Followup recordings on 5 animals revealed that 24 hr after the last injection of kryptopyrrole 4 of the rats were still exhibiting sporadic periods of high voltage hypersynchronous EEG. Recordings made one week following the last kryptopyrrole injection were free of hypersynchronization in all 5 of these animals.

In most records the appearance of high voltage hypersynchronization occurred simultaneously at all 3 recording sites. There were, however, some exceptions to this finding. Rats 20 and 8, for example, both had electrodes placed in the cortex, dorsal hippocampus, and mesencephalic reticular formation. In both cases the recordings from the dorsal hippocampus did not exhibit bursts of high voltage synchronization while this pattern was present at cortical and reticular formation sites. Rat 122 also presented a site-specific EEG record. This animal had recording sites in the lateral hypothalamic area, lateral amygdaloid area, and corticospinal tract. The only site in this array showing bursts of high voltage hypersynchronized EEG was the lateral amygdaloid area.

Abnormal EEG Spiking

Eight of the 10 rats exhibited abnormal spiking activity after the first injection of kryptopyrrole. These patterns were reminiscent of spike and wave patterns observed during epileptic seizures [19], although the observed frequency of 1–2 Hz is slower than the 3 Hz activity usually observed in spike and wave epileptic patterns. The two rats which did not show this activity after the first injection had both received 15 μl/kg of kryptopyrrole. All of the 10 animals presented abnormal spiking at some point in the study. Fig. 4 presents examples of kryptopyrrole-induced spiking EEG patterns. In most records the appearance of the rhythmical spiking occurred simultaneously at all 3 recording sites. There were some exceptions to this finding, however, Rat 122 showed this pattern only at the lateral amygdaloid site. In this animal, recordings from the lateral hypothalamic area and corticospinal tract showed neither spiking nor periods of high voltage hypersynchronous EEG. Rat 8 also showed site-specific effects: EEG spiking occurred at cortical and hippocampal sites but not at the reticular formation. The abnormal EEG patterns occurred from 15 to 30 min after administration of kryptopyrrole.

The animals did not appear to develop tolerance to the kryptopyrrole induced spiking EEG. This EEG pattern continued to occur sporadically as long as the animals were given kryptopyrrole. Recordings made 24 hr following the last injection continued to show these patterns, but recordings made one week following the last injection were free of abnormalities.

Behavioral Abnormalities

Marked behavioral alterations were consistently observed following the initial injection of kryptopyrrole. Behavioral effects included ataxia, hyperventilation, locomotor depression and catalepsy. In many animals a marked ataxia was observed as rapidly as five to ten minutes following abdominal administration of kryptopyrrole. Throughout the course of the study frequent examples of catalepsy were observed. Animals would frequently adopt unusual and strained postures and remain motionless for several minutes.

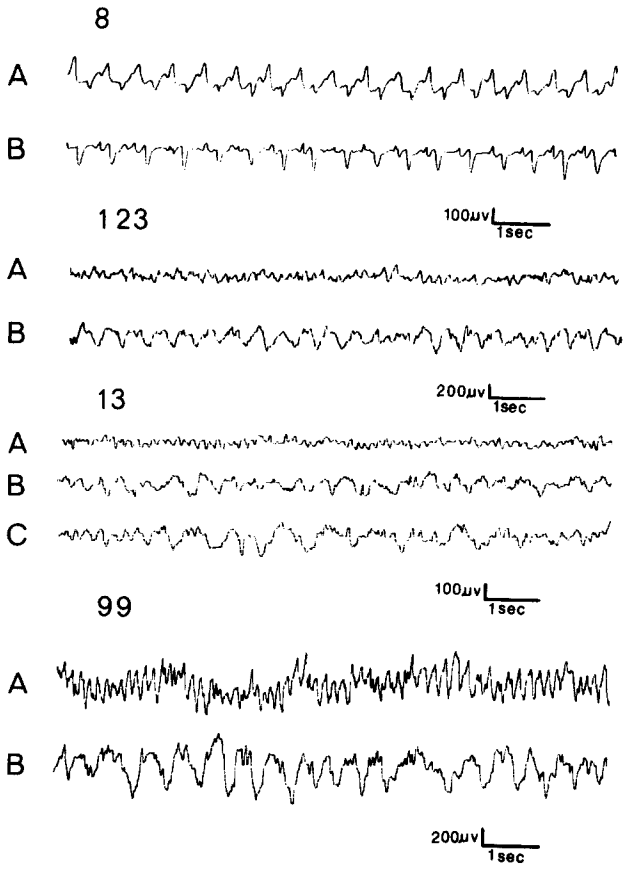

FIG. 4. Kryptopyrrole-induced high voltage, rhythmical spiking EEG patterns. Rat 8: A, dorsal hippocampus, 60 min following 20 μl/kg; B, dorsal hippocampus, 65 min following 20 μl/kg. Rat 123: A, anterior hypothalamic area, 10 min after introduction into chamber, no-drug baseline recording; B, anterior hypothalamic area, 10 min after 15 μl/kg. Rat 13: A, mesencephalic reticular formation, 15 min after introduction into chamber on baseline recording; B, mesencephalic reticular formation, 15 min after 25 μl/kg; C, mesencephalic reticular formation, 15 min after 70 μl/kg. Rat 99: A, no-drug baseline recording, caudate nucleus 60 min after introduction into chamber; B, caudate nucleus, 60 min after 30 μl/kg.

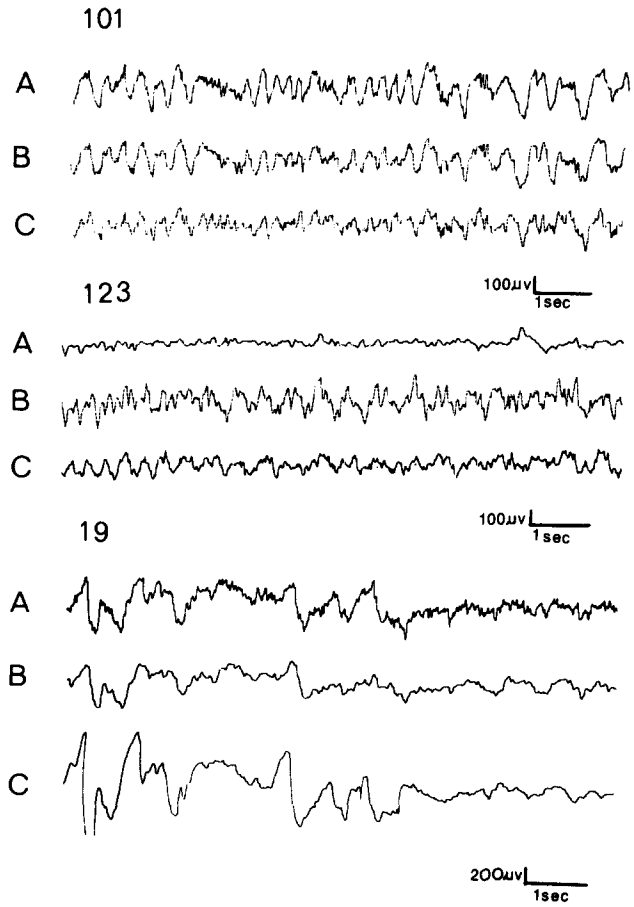

FIG. 5. EEG patterns associated with periods of ataxia, catalepsy, and hyperreactivity. Rat 101: A, lateral septal nucleus, 10 min following 15 μl/kg, cataleptic behavior; B, caudate nucleus, 10 min following 15 μl/kg, cataleptic behavior; C, lateral geniculate body, 10 min following 15 μl/kg, cataleptic behavior. Rat 123: A, median amygdaloid area, 10 min following 40 μl/kg, during ataxia; B, posterior thalamic nucleus, 10 min following 40 μl/kg, during ataxia; C, anterior hypothalamic area, 10 min following 40 μl/kg, during ataxia. Rat 19: A, cortex, 45 min following 15 μl/kg, during hyperreactivity; B, dorsal hippocampus, 45 min following 15 μl/kg, during hyperreactivity; C, mesencephalic reticular formation, 45 min following 15 μl/kg, during hyperreactivity.

Three occurrences of an extremely unusual behavioral reaction were observed in the course of the study. Rat 13 exhibited periods of hyperreactivity in which it jumped up quickly from a reclining position, moved rapidly into a corner of the test chamber, arched the back, and raised the front paws in front of the head. The entire response sequence persisted for approximately 60 sec. This rat had received 20 μl/kg of kryptopyrrole 60 min prior to showing the behavioral reaction. Rat 19 showed two similar behavioral reactions following kryptopyrrole injection. Following the appearance of this atypical response, the entire recording system and test chamber were tested to check the possibility that the animal had received either foot shock or feedback through the electrodes. No such feedback was ever detected. Additional studies in progress have indicated that animals receiving no injection, no electrode implantations, and rats receiving only saline injections have never shown this behavioral reaction in our laboratory apparatus. Behavioral studies in progress in our laboratory have demonstrated the presence of similar reactions in other rats receiving kryptopyrrole.

The most frequent EEG correlate of unusual motor responses was the simultaneous occurrence of abnormal spiking. In most cases where ataxia was noted on the EEG record, the spiking EEG pattern was also present. Cataleptic postures were also associated with the occurrence of spiking EEG patterns. The periods of hyperreactivity observed in Rats 13 and 19 were associated with high voltage spiking EEG patterns. Fig. 5 presents examples of EEG activity observed during periods of ataxia, catalepsy, and hyperreactivity.

Rat 8 was found dead in its home cage following the second consecutive daily injection of 20 μl/kg kryptopyrrole. At autopsy the chest cavity was found to be filled

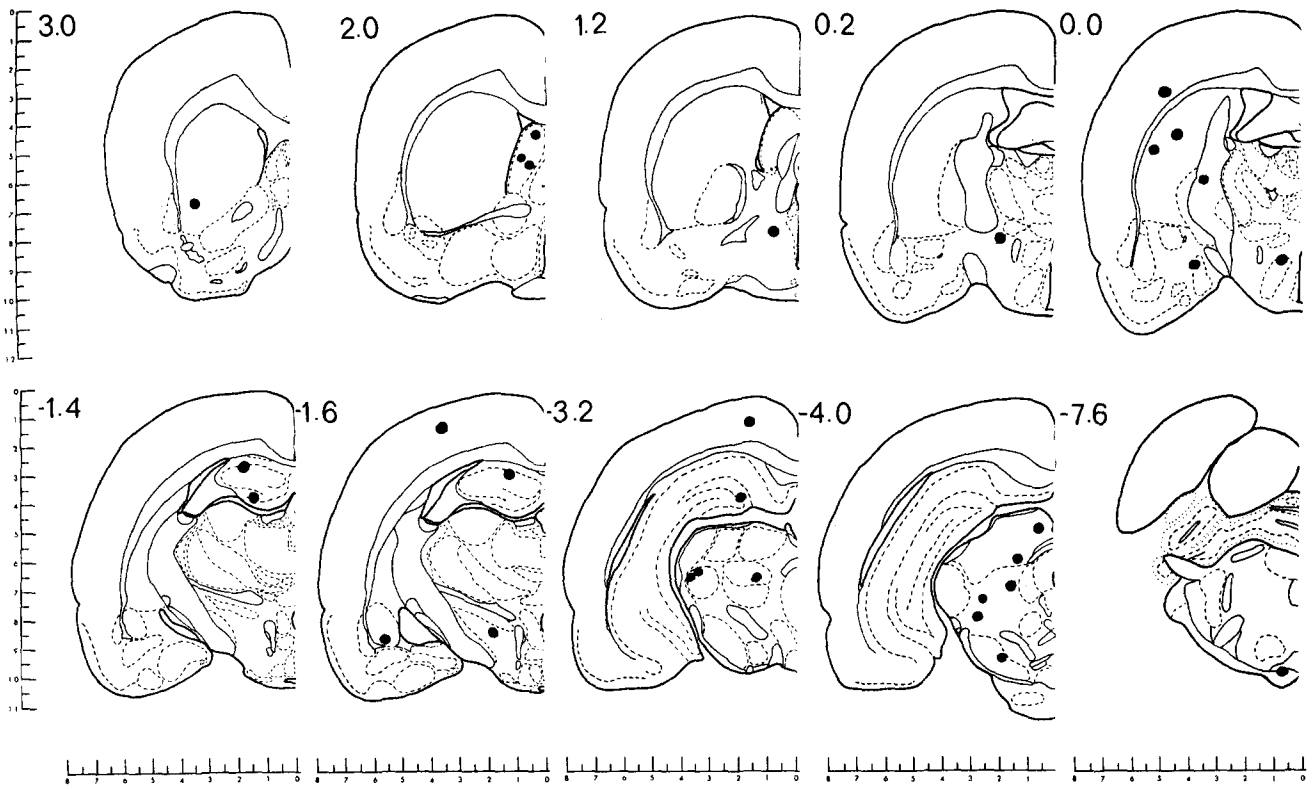

FIG. 6. Summary of the recording locations as verified by histological examination. The dark points indicate the location of the tip of the electrode. The rostral-caudal coordinate is noted at the top of each section and refers to Bregma. Outlines are adapted from the atlas of Pellegrino and Cushman [14].

with a clear, viscous fluid. Following the completion of the study, the brains were prepared for histological verification of electrode locations. Figure 6 shows the results of the histology for the ten rats.

DISCUSSION

The results of these studies show that injections of 9.1 to 82 mg/kg of kryptopyrrole decreases EEG voltage, disrupts synchronization and induces abnormal spiking activity at a variety of cortical and subcortical sites in rat brain. Chronic daily administration of kryptopyrrole resulted in the development of tolerance, with the EEG showing a tendency for voltage to return to baseline levels. Animals receiving incremental dosages of kryptopyrrole after voltage tolerance was established consistently showed reduced voltage levels over the prior recording days. Kryptopyrrole was also observed to disrupt synchronized EEG activity at all of the recording sites. The kryptopyrrole-induced asynchronous activity did not appear to habituate with chronic administation of the drug.

Another drug-induced EEG phenomenon observed in these experiments was the occurrence of intermittent periods of low frequency hypersynchronous activity. These hypersynchronous waves bear a strong resemblance to the hypersynchronous EEG paterns observed in man during hallucinatory states induced by LSD-25, psilocybin, and mescaline [5]. Similar EEG wave patterns have also been observed in cats given LSD-25 [1]. Winters and Wallach [19] suggest that cats exhibiting the slow frequency intermittent hypersynchronization associated with hallucinogenic agents show a loss of contact with the environment simultaneously with the presence of these EEG waves.

The rhythmical spiking activity illustrated in Fig. 4 was observed in all of the animals given kryptopyrrole. This abnormal EEG pattern was found to be consistently induced by kryptopyrrole and illustrates its toxic effect on the brain. Our experiments suggest that the animals did not appear to develop tolerance to the drug-induced rhythmical spiking. These patterns continued in the records as long as kryptopyrrole was administered. Recordings made one week following the last administration of kryptopyrrole were free of abnormalities.

The findings from these experiments are in agreement with other work [11] demonstrating the toxicity of kryptopyrrole on the pleural cavity and the central nervous system. Our laboratory has consistently found that the potential lethality of kryptopyrrole is decreased if the animal is first primed with doses below 20 μl/kg. In the present experiments, and in additional work in progress, initial doses of 20 μl/kg, or more, have often been found to cause severe toxic reactions and or death.

In the context of a drug-induced model of psychoses, it is interesting that all doses of kryptopyrrole used in these experiments induced numerous examples of cataleptic behavior. During these episodes the animal would typically adopt a strained or bizarre posture and remain motionless in this pose for several minutes. One animal, for example, stood in the middle of the test chamber on its hind legs with its nose touching the top of the cage. The animal

retained this posture for nine minutes. Other behavioral abnormalities induced by kryptopyrrole included ataxia, hyperventilation, and locomotor depression. In most cases where ataxia, catalepsy, and hyperventilation were observed, the EEG indicated the simultaneous occurrence of high voltage, rhythmical spike patterns. The limited literature available on the effects of kryptopyrrole on the mammalian body suggests that the drug has a powerful depressant effect on the CNS and behavior [11, 12, 15, 16]. The present results also suggest a powerful behavioral-motor depressant effect as evidenced by the locomotor depression and numerous cataleptic periods consistently associated with kryptopyrrole.

Hoffer and Osmond [6] have proposed that mauve factor, now believed to be kryptopyrrole, represents a metabolic anomaly that is associated in an etiological fashion with certain psychiatric conditions, particularly schizophrenia. They maintain that the disappearance of this biochemical anomaly is statistically associated with psychiatric improvement. The results of the present study strengthen the Hoffer-Osmond hypothesis by demonstrating that the introduction of kryptopyrrole into the mammalian body is behaviorally and electrophysiologically disruptive. The abnormal behavioral reactions and EEG patterns associated with kryptopyrrole provide evidence that this compound has a serious detrimental effect on normal brain function. These kryptopyrrole-induced alterations bear some similarity to various behavioral patterns associated with psychiatric conditions and EEG patterns in humans elicited by hallucinogenic drugs.

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