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Relationship Between Amphetamine-Induced Effects on EEG Power Spectra and Motor Activity in Rats

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YOUNG, G. A. *Relationship between amphetamine-induced effects on EEG power spectra and motor activity in rats.* PHARMACOL BIOCHEM BEHAV 30(2) 489–492, 1988.—Amphetamine injection (2.5 mg/kg, SC) produced a significant quadratic trend in mean peak EEG frequencies in the theta band in one group of rats. Progressive increases in peak EEG frequencies occurred for approximately 30 min after amphetamine injection and were followed by progressive decreases through 100 min. These changes in peak EEG frequencies may have reflected pharmacokinetic properties of amphetamine. A significant and similar quadratic trend was seen in mean motor activity counts after amphetamine injection in a second group of rats. In addition, a significant positive correlation was found between amphetamine-induced effects on peak EEG frequencies and mean motor activity counts.

Amphetamine EEG power spectra Motor activity

SPONTANEOUS electroencephalograms (EEGs) have been used extensively to study and assess effects of drugs upon the brain [4]. In our laboratory we have used EEG and behavioral correlates during opioid self-administration in rats to delineate opioid pharmacodynamic and pharmacokinetic properties [23]. For example, unique characteristics of levo-alpha-acetylmethadol (LAAM) were attributed to its N-demethylated metabolites, nor-LAAM and dinor-LAAM [26–28]. Pharmacodynamic differences between the effects of *kappa* opioid withdrawal and morphine withdrawal on EEG and behavior have been demonstrated [21].

Although the use of EEGs has provided pertinent information, recent computer analysis techniques have been developed that provide quantitative characterization of EEG activities, which have allowed experimenters to more easily assess both subtle and complex EEG changes produced by drugs and chemicals. One of these techniques generates EEG power spectral density arrays based upon the estimation of a complex Fourier series from an EEG epoch [8]. Later, a fast Fourier transformation (FFT) expressed by a single algorithm provided a means to derive EEG power spectra very efficiently with high-speed digital computers [6,18].

In our laboratory we have also used drug-induced changes in EEG power spectra to delineate pharmacodynamic and pharmacokinetic properties of CNS-active drugs and chemicals [10,24]. We have utilized EEG power spectra to investigate pharmacological phenomena such as tolerance, cross-tolerance, physical dependence, receptor selectivity and stereospecificity. For example, in comparative studies of the opioids morphine (*mu* agonist), ketocyclazocine (*kappa* agonist) and SKF-10,047 (*sigma* agonist), differential and stereospecific effects on EEG power spectra and behavior were shown [22,25]. Moreover, characteristic pharmacodynamic changes in EEG power spectra were produced by ethanol [20,29] and Δ^9-THC [5], and the neurotoxic substances lead [12], trimethyltin and kainic acid [15,16].

In the present study the effects of amphetamine on EEG power spectra and motor activity were studied. One objective of the study was to assess whether amphetamine-induced EEG power spectra might provide pharmacokinetic information. A second objective was to assess any relationships between amphetamine-induced changes in EEG power spectra and motor activity.

METHOD

Animals

Female Sprague-Dawley rats (225–275 g) were used. For studies of amphetamine-induced EEG changes, rats were implanted with bipolar epidural frontal (2 mm anterior and 2 mm lateral to bregma) and parietal (3 mm posterior and 2 mm lateral to bregma) EEG, and temporalis electromyographic (EMG) recording electrodes. Surgical procedures have been previously described [9].

EEG Recording and Spectral Analyses

Rats were housed in individual chambers, 30.5×30.5×66.0 cm. To permit free movement of the rat, each cage was equipped with a swivel connector having concentric mercury pools which served as noise-free sliding contacts [11]. These freely moving rats were allowed to acclimatize to the experimental cages for two to three days before experimentation.

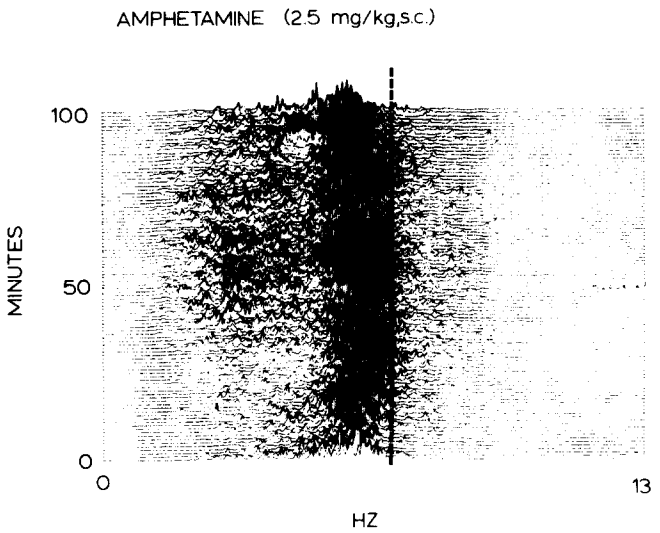

FIG. 1. Sequential EEG power spectra are shown following subcutaneous injection of amphetamine (2.5 mg/kg) in an individual rat.

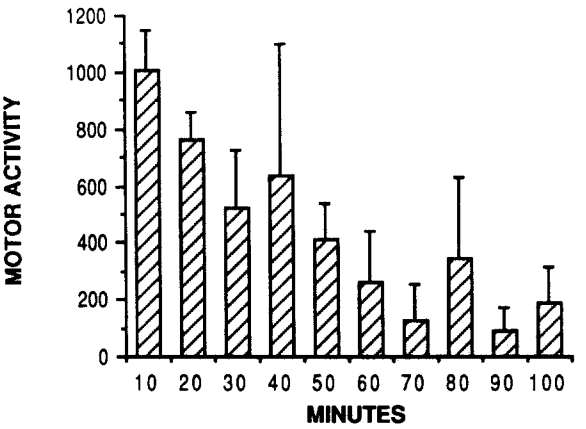

FIG. 2. Grouped data showing mean motor activity counts ±s.d. as a function of time after control saline injection.

For each rat, direct EEG activity was filtered to pass frequencies between 1 and 35 Hz. The EEG and integrated EMG activities were continuously recorded on a Grass polygraph.

Power spectral analyses of EEG were performed offline, using a Nicolet MED-80 minicomputer system [10, 24, 30]. Sequential EEG power spectra were obtained every min by averaging spectra derived from six consecutive 10-sec epochs of cortical EEG that were digitized at a sampling rate of 52/sec, and power spectral densities were estimated at 0.1 Hz intervals from zero to 25 Hz. For grouped data, sequential EEG power spectra were obtained every 10 min by averaging spectra derived from 60 consecutive 10-sec epochs of cortical EEG.

Motor Activity Measurements

Horizontal activity was measured with a Digiscan Optical Activity Monitor (Model RXY5L). Activity chambers were circular with a diameter of 30.5 cm.

Drugs

Amphetamine hydrochloride (Sigma Chemical Co., St. Louis, MO) was dissolved in sterile water and administered SC in a volume of 0.1 ml. Ketamine hydrochloride (Ketalar, Parke-Davis Div. of Warner-Lambert Co., Morris Plains, NJ) was used to induce anesthesia.

Procedure

In the EEG study, four rats were injected with amphetamine (2.5 mg/kg, SC) and EEG activities were simultaneously recorded on a polygraph and FM tape using a Hewlett-Packard model 3960-A recorder. Four control rats were injected with saline (0.1 ml/rat, SC).

In the motor activity study, four rats were injected with amphetamine (2.5 mg/kg, SC) and individually placed in the activity monitor immediately after injection. Activity readings were obtained at 10 min intervals. Four control rats were injected with saline (0.1 ml/rat, SC).

Statistics

Mean peak EEG frequencies and mean motor activity counts were subjected to one-way analyses of variance with repeated measures, followed by tests for trends [19]. A linear regression was calculated with the least squares method and a Pearson r product-moment correlation coefficient was obtained.

RESULTS

Amphetamine (2.5 mg/kg, SC) produced continuous predominant increases in EEG spectral power in the 6–8 Hz range (theta frequencies or RSA) for approximately 100 min (Fig. 1). The mean peak frequencies in the 6–8 Hz range gradually increased during the first 30 min after injection and then gradually decreased during the last 50 min.

Rats receiving control saline demonstrated an emergence of EEG and behavioral slow-wave sleep episodes at an average of 27±5 (mean±s.d.) min after injection. Slow-wave sleep EEG was associated with a predominance of spectral power in the lower frequency range (zero to 5 Hz) and a gradual diminution of spectral power in the 5–10 Hz range. Thereafter, control rats cycled among the states of slow-wave sleep, rapid eye movement sleep and wakefulness.

Grouped data showing mean peak EEG frequencies as a function of time after amphetamine injection are shown in Fig. 3A. There were significant differences in mean peak EEG frequencies, $F(9,27)=2.68$, $p<0.05$. Statistical tests on trends indicated significant linear, $F(1,27)=102.68$, $p<0.01$, quadratic, $F(1,26)=55.65$, $p<0.01$, and cubic, $F(1,25)=20.40$, $p<0.01$, components. Observations of these rats indicated that amphetamine produced almost continuous behavioral activation consisting of locomotion, rearing and head movements. There were mimimal brief occurrences of stereotypic behaviors such as chewing and licking.

Control rats receiving saline displayed a peak mean increase in motor activity during the first ten min, after which mean motor activity counts steadily declined over the remaining 90 min of observation (Fig. 2).

Grouped data showing mean motor activity counts as a function of time after amphetamine injection are shown in Fig. 3B. There were significant differences in mean motor activity counts, $F(9,27)=2.65$, $p<0.05$. Statistical tests on

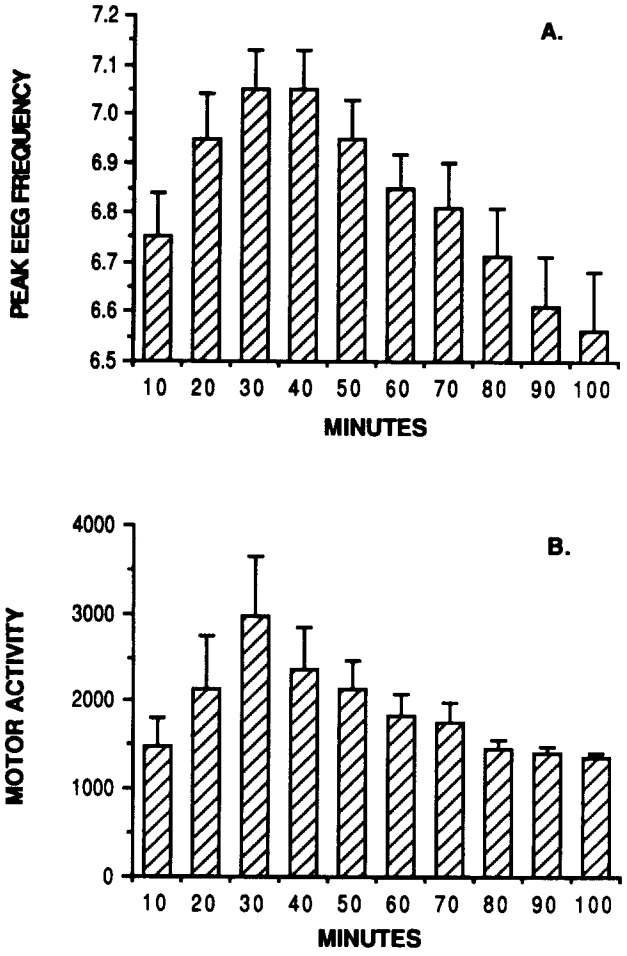

FIG. 3. Grouped data showing mean peak EEG frequencies ±s.d. (A) and mean motor activity counts ±s.d. (B) as a function of time after amphetamine injection.

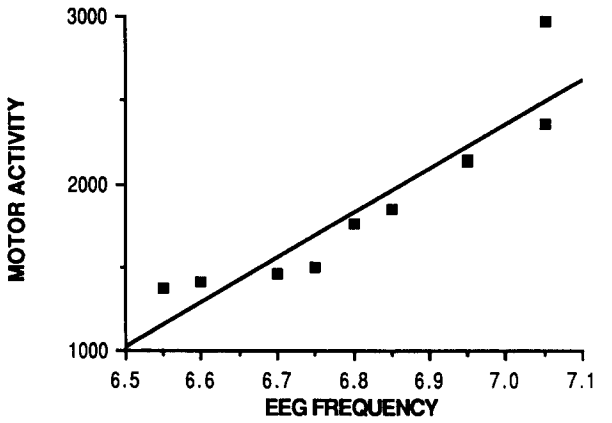

FIG. 4. Scatter plot and linear regression line showing relationship between amphetamine-induced effects on mean peak EEG frequencies and mean motor activity counts.

trends indicated significant linear, $F(1,27)=10.30$, $p<0.01$, and quadratic, $F(1,26)=7.15$, $p<0.05$, components.

The relationship between mean peak EEG frequencies and mean motor activity counts is shown in Fig. 4. There was a positive linear correlation between mean peak EEG frequencies and mean motor activity counts, $r=.922$, which was significant, $t(8)=6.735$, $p<0.001$. The linear regression equation was $Y = 16200 + 2650X$.

DISCUSSION

Amphetamine administration in rats produced a significant quadratic trend in mean peak EEG frequencies in that increases in mean peak EEG frequencies in the theta band were seen during the first 30 min after injection, and, thereafter, decreases were seen for up to 100 min after injection. The demonstrated shifts in peak EEG frequencies, as delineated by spectral analyses, may be indicative of pharmacokinetic properties of amphetamine. For example, the maximal increase in peak EEG frequencies occurring at approximately 30 min after amphetamine injection may represent the time of peak amphetamine effect on brain processes or the time of peak amphetamine brain levels. The duration of continuous EEG theta waves after amphetamine injection may represent duration of action of amphetamine-induced effects on brain processes.

The theta frequencies recorded in the present study were derived from electrodes placed over the cortex. When EEG activities have been recorded simultaneously from the cortex and hippocampus in rats, certain cortical electrode locations have been shown to pick up theta wave frequencies that are of hippocampal origin [3,17]. The posterior cortical electrode locations used in the present study are located over the hippocampus, and, thus, were most likely also recording theta wave activity originating from the hippocampus.

A significant quadratic trend was also seen in mean motor activity counts after amphetamine injection. In addition, a highly significant positive correlation, $r=.992$, $p<0.001$, was found between amphetamine-induced effects on mean peak EEG frequencies and mean motor activity counts. In a review of relationships between hippocampal EEG and behavior in the waking rat [14], it was concluded that hippocampal theta activity is highly correlated with motor behaviors such as walking, rearing, head movements or swimming, while hippocampal large irregular activity accompanied behavioral immobility, and more "reflexive" behaviors such as chewing, shivering or grooming. Behavioral measurements that were made after amphetamine administration [7,13] suggest that a 2.5 mg/kg dose of amphetamine would primarily produce the above types of motor behavior that would be associated with hippocampal theta activity.

The demonstrated shifts in peak EEG frequencies may be indicative of the speed or intensity of motor behavior [1,2]. Thus, measurements of horizontal activity may have reflected measurements of speed or intensity of motor activity produced by amphetamine.

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