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Morphine Self-Administration and EEG Power Spectra in the Rat[1]

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YOUNG, G. A., G. F. STEINFELS, N. KHAZAN AND E. M. GLASER. *Morphine self-administration and EEG power spectra in the rat.* PHARMAC. BIOCHEM. BEHAV. 9(4) 525–527, 1978.—Power spectral analyses were used to study changes in cortical EEG during morphine self-administration in freely-moving dependent rats prepared with chronic cortical and muscle electrodes and with permanent indwelling IV cannulae. As time progressed from a morphine self-injection toward another injection, a significant spectral shift of the EEG to lower frequencies occurred during successive REM sleep episodes. Each morphine self-injection reinstated the predominance of higher frequencies in the EEG spectra. These EEG changes which preceded lever pressing may reflect changes in morphine plasma levels and in the state of the CNS that precede drug-seeking behavior.

EEG Power spectra Morphine self-administration

THE PATTERN of morphine self-administration in morphine-dependent rats has been previously described. It was shown that morphine-dependent rats with free access to an operant lever for self-administration usually take single IV injections (10 mg/kg) every 2 to 3 hr [19]. In these studies drug-seeking behavior as expressed by lever pressing usually emerged towards the end of each interinjection interval. The electroencephalographic (EEG) correlates and distribution of awake, sleep, and rapid eye movement (REM) sleep episodes during these interinjection intervals have also been delineated [11, 12, 14]. Each self-injection of morphine in the morphine-dependent rat was shown to produce a brief behavioral stupor associated with EEG slow-bursts which was followed by behavioral and EEG arousal. Sleep and REM sleep episodes then predominated until the next injection which, in turn, initiated another interval with similar patterns of sleep-awake distribution.

The effects of morphine on EEG have also been studied with the use of voltage integrators. It has been found that acute morphine injections produced increases in the EEG "mean energy content" in the rabbit [5] while a decline in the mean integrated EEG voltage occured during morphine abstinence in the rat [10]. Computer analyses have been employed to elucidate EEG changes produced by several psychoactive drugs in the monkey [3,4], cat [15], rabbit [20] and man [2, 6, 7, 8, 13].

As a consequence of our earlier studies [10, 11, 12, 14, 19], we have entertained a hypothesis that there might be particular quantitative EEG changes associated with drug-seeking behavior in the dependent rat self-administering morphine. A mini-computer, Nicolet MED-80 system, was used in our search for such EEG changes. We studied and compared the EEG power spectra derived from successive episodes of REM sleep EEG occurring between morphine self-injections in dependent rats. Previous data from our laboratory have shown that the power spectra associated with REM sleep episodes in a drug-free rat are associated with minimal variability [21].

METHOD

Five adult female Sprague-Dawley rats were prepared with chronic cortical EEG and temporalis muscle, electromyographic (EMG) electrodes [9]. Bipolar cortical stainless steel electrodes were implanted over the frontal cortex (2 mm anterior and 2 mm lateral to bregma) and the ipsilateral parietal cortex (3 mm posterior and 2 mm lateral to bregma). An additional screw was placed 6 mm posterior and 2 mm lateral to bregma and served as the indifferent electrode. For drug injections, a silicone rubber cannula was implanted into the right external jugular vein [17,18]. Each rat was maintained in an individual cage that was equipped

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with a response lever, a swivel cable connector for EEG and EMG recordings, and a feed-through cannula for drug administration. EEG and EMG activities were recorded on a Grass Model 7D polygraph. The EEG was filtered to pass frequencies between 1 and 30 Hz, and was recorded on FM tape with a Hewlett-Packard Model 3960-A recorder. One channel recorded a time code that was generated with a Datatron Model 3950 Translator/Generator.

Rats were first made tolerant to and physically dependent on morphine by a series of electronically-controlled automatic IV injections. During the first day rats received 1.25 mg/kg/hr of morphine. The dose was increased to 2.5, 5.0, 10.0 and 20.0 mg/kg/hr on successive days. Each rat was then trained to lever press on a fixed ratio (FR) schedule of reinforcement to receive morphine. A FR of 1 lever press was initially required per injection, which was gradually increased to FR-20. Behavioral states of sleep, REM sleep, and wakefulness were identified by the corresponding changes in EEG and EMG recordings [11, 12, 14, 19].

EEG recordings of the successive REM sleep episodes occurring between morphine injections were processed as follows. Using a Nicolet MED-80 system, power spectra derived from EEG during each REM sleep episode were obtained. REM sleep episodes varied in duration from 30 sec to 4 min. Data were digitized at a sampling rate of 54/sec and power spectral densities from 0 to 27 Hz were estimated at 0.1 Hz intervals and weighted geometric smoothing over three neighboring frequencies were used.

RESULTS

A typical pattern of distribution of sleep-awake behavior during a morphine interinjection interval with a morphine-dependent rat is shown in the right side of Fig. 1. Following lever pressing and morphine self-administration the rat remained awake for about an hour. This awake period was followed by alternations of sleep, REM sleep, and wakefulness for approximately the next 75 min. Finally, the rat pressed the lever on the FR-20 schedule of reinforcement and received the next morphine injection. Power spectra of the successive REM sleep episodes occurring during this interinjection interval are shown in the left side of Fig. 1. It was found that the EEG spectra of the last REM sleep episode prior to the next self-injection had a lower peak frequency (6.9 Hz) than the first spectra (7.8 Hz) that occurred in this interinjection interval.

This phenomenon of the slowing of the peak frequency of the EEG during successive REM sleep episodes in a morphine interinjection interval was detected in all 5 rats studied. The EEG of 16 morphine interinjection intervals were collected on FM tape and analyzed. Eleven of these intervals were associated with a slowing of the EEG peak frequency during the latter REM sleep episodes; in all these cases 90% or more of the lever pressing activity for morphine injections emerged after the last REM sleep episodes. In these 11 cases, the last REM sleep episodes were less than 10 min from the next morphine self-injections. Three intervals which showed no slowing of the EEG frequency were of unusual short duration with scattered lever pressing activity. The other 2 intervals were associated with REM sleep episodes that occurred more than 30 min prior to self-injections.

Further analyses were done with interinjection intervals of 2 hr or longer that had REM sleep episodes within the last 10 min. For all 5 rats a decline in the mean peak frequency

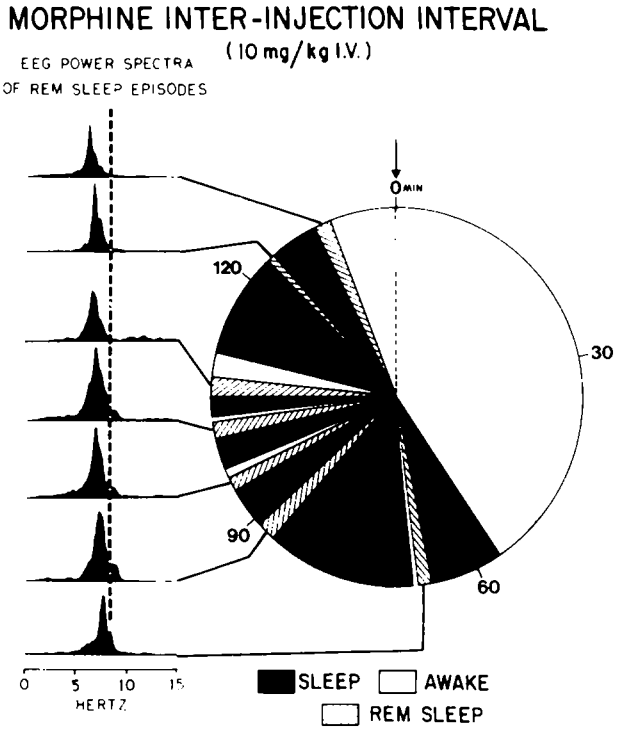

FIG. 1. The pattern of distribution of sleep-awake behavior in an individual morphine-dependent rat during a morphine interinjection interval is shown in the right portion of the figure. Successive power spectra derived from cortical EEG samples during each occurrence of REM sleep are shown in the left portion of the figure. The successive occurrences of REM sleep proceed from the bottom to the top of the figure. Spectral power is presented as a function of frequency.

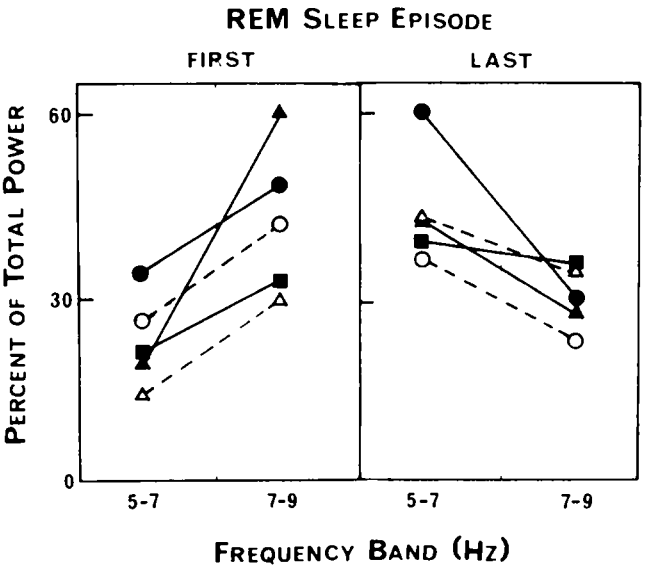

FIG. 2. The percent of total power is shown as a function of the 5-7 Hz and 7-9 Hz bands (theta wave range). Data is presented for the first and last occurrences of REM sleep episodes during morphine interinjection intervals for each of the 5 rats.

from 7.70 Hz during the first REM sleep episodes to 7.05 Hz during the last REM sleep episodes occurred. This difference is significant ($t=6.60$, $df=4$, $p<0.01$). Figure 2 shows the percent of total power as a function of the 5–7 and 7–9 Hz bands for the first and last REM sleep episodes during morphine self-injections for each of the 5 rats. It was found that there was more spectral power in the 7–9 Hz band than the 5–7 Hz band during the first REM sleep episodes for all 5 rats. In contrast, there was more spectral power in the 5–7 Hz band during the last REM sleep episodes for all 5 rats. In a treatments×treatments×subjects analysis of variance for this data, the interaction factor was significant, $F(1,4)=20.65$, $p<0.01$. This indicates that the distributions of spectral power in the 5–9 Hz band between the first and the last REM sleep episodes in an interinjection interval were different.

DISCUSSION

In morphine-dependent rats a significant shift of EEG spectral power in the 5 to 9 Hz range to lower frequencies was observed in the REM sleep episodes occurring just before morphine self-injections. Morphine self-administration reinstated spectral power to relatively higher frequencies. In a recent report, it has been shown that acute intraventricular doses of $ACTH_{1-10}$ and β-endorphin produced similar shifts in spectral power derived from hippocampal EEG during the first REM sleep episodes following treatment in rats [1]. Our study showed that 90% or more of the lever pressing for the next self-injection of morphine occurred after the last REM sleep episode where the slowing of the EEG frequency was observed. It is therefore suggested that the slowing of the REM sleep EEG frequency which occurred late in morphine interinjection intervals may reflect changes in morphine plasma levels and in the state of the CNS that precede drug-seeking behavior. The slowing of the EEG persisted during a short period of extinction when the injection pumps were turned off for the next 3 hr. When the pumps were turned back on, morphine self-injections reinstated the higher frequency spectra of the REM sleep EEG. Preliminary data during methadone self-administration have also demonstrated similar shifts in EEG frequency and spectral power like those that occurred during morphine self-administration [16].

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