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Research Report

EEG activities in the orbitofrontal cortex and dorsolateral prefrontal cortex during the development of morphine dependence, tolerance and withdrawal in rhesus monkeys

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Abstract

Investigating the activities of the prefrontal cortex (PFC) in the process of addiction is valuable for understanding the neural mechanism underlying the impairments of the PFC after drug abuse. However, limited data are obtained from primate animals and few studies analyze Electroencephalogram (EEG) in the gamma band, which plays an important role in cognitive functions. In addition, it is yet unclear whether drug abuse affects the orbitofrontal cortex (OFC) and dorsolateral PFC (DLPFC) – the two most important subregions of the PFC – in similar ways or not. The aim of this study is to address these issues. We recorded EEG in the OFC and DLPFC in three rhesus monkeys. All animals received a course of saline (NaCl 0.9%, 2 ml) injection (5 days) followed by 10 days of morphine injection (every 12 h), and then a further series of saline injection (7 days). A main finding in the present study was that morphine decreased EEG power in all frequency bands in a short period after injection in both the OFC and DLPFC in monkeys. And gamma power decreased not just in short period after morphine injection but lasted to 12 h after injection. Moreover, we found that although the changes in EEG activities in the OFC and DLPFC at 30–35 min after injection were similar, the DLPFC was more sensitive to the effect of morphine than the OFC.

Theme: Neural basis of behavior
Topic: Drugs of abuse: opioids and others

Keywords: Addiction; Prefrontal cortex; Morphine; Monkeys; EEG

1. Introduction

Drug addiction is a problem of complex, compulsive drug administration [17,23]. Accumulated studies have indicated that the prefrontal cortex (PFC) plays a key role in drug abuse. It has been demonstrated that the PFC is a target of drug abuse. Previous studies have found that opioids can affect neuronal activity in the PFC: most of spontaneous firing is inhibited and cells exhibit morphine-associated attenuation of activation response to glutamate [12,13]. And acute nicotine administration can change the levels of neurotransmitters, such as dopamine, serotonin and norepinephrine in the PFC [27]. Moreover, using positron emission tomography (PET) neuroimaging techniques, cocaine-induced activation of the PFC has been found [16].

On the other hand, previous efforts involving cognitive and brain-imaging studies have demonstrated that repeated drug abuse can produce the disruption of cognitive functions mediated by the PFC, such as decision making, response inhibition and planning [18]. Furthermore, previous studies

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have found that there is also a structural impairment of the PFC caused by drug abuse. For example, using structural magnetic resonance imaging (MRI), a reduction of PFC volume has been found in cocaine addicts [9]. Although the role of the PFC in drug abuse has been noted for a long time, the interaction between drug abuse and the PFC remains elusive.

The PFC is the most evolved cerebral cortex in primates. It can be divided into several subregions with different anatomical and functional characters. To drug abuse, the two PFC regions that have received the most attention are the orbitofrontal cortex (OFC) and dorsolateral PFC (DLPFC). The OFC is interconnected with other brain areas known to be involved with the reinforcing effects of drug abuse, such as ventral tegmental area, nucleus accumbens, amygdala and hippocampus. And the DLPFC is connected with the OFC, amygdala and hippocampus [14,26]. Previous studies have showed that drug abuse can lead to impairments of the two areas. For example, most of addicts and patients with damage to the OFC showed similar behaviors in decision making: when faced with a choice to pursue a course of action that brings an immediate reward at the risk of incurring future negative consequences, they chose the immediate reward and ignored the future consequences [2,3,5]. Addicts also showed below normal levels of performance on the measure of working memory in which the DLPFC is crucial [4]. However, the specific roles played by the OFC and DLPFC in the process of addiction are unclear. Also, we do not know whether drug abuse affects the OFC and DLPFC in similar ways or not.

Electroencephalogram (EEG) is a sensitive measure to study the activity of brain. Evidence is presented that EEG activity is associated with many important functions, such as learning and memory. Especially, it is increasingly documented that gamma band (20–100 Hz) plays an important role in cognitive functions. Previous studies in a series of nonprimate animals (such as rats, rabbits, cats and dogs) have demonstrated that EEG activities are altered during the development of drug dependence and tolerance [6,15,20,29]. However, limited data have been obtained from primate animals and few studies have analyzed EEG in the gamma band.

Therefore, we recorded EEG in the OFC and DLPFC during the development of morphine dependence, tolerance and withdrawal in rhesus monkeys to get a further understanding about the changes in EEG activities of the PFC in the process of morphine addiction.

2. Materials and methods

2.1. Subjects

The experimental subjects were 3 adult female rhesus monkeys (*Macaca mulatta*) weighing 4.0–6.0 kg. The animals were housed in individual cages in a temperature-controlled (25 °C) colony room with food and water available. This study was performed in accordance with the 'Principals of laboratory animal care' (NIH) and institutional guidelines.

2.2. Surgery

Twelve hours before surgery, each animal was restricted from food and water. The surgery was performed aseptically. The monkeys were anesthetized with sodium pentobarbital (10 mg/kg, i.m.) following premedication with hydrochloric acidulated ketamine (15 mg/kg, i.m.) and placed in a stereotaxic apparatus. During the operation, sodium pentobarbital anesthesia was maintained and supplementary doses were administered as needed. The scalp was incised and retracted along with the muscles overlying the skull. The surface of the skull was cleaned of all fasciae and then thoroughly dried. One Teflon-insulated epidural stainless steel recording electrode was threaded into the skull overlying the right DLPFC (dorsal part of area 46), and one depth electrode was placed in the ipsilateral OFC (area 13). All the electrodes were soldered to a female connector fixed to the skull by dental cement. Electrode locations were verified according to X-ray examination in coronal, sagittal and horizontal angles. After surgery, the electrode locations were reconfirmed by X-ray examination.

2.3. Drug administration

One month of recuperation was allowed after surgery. Experiments were performed in a soundproof room. To habituate the animals to the recording conditions, on seven consecutive days before the experiment, they were placed in a primate chair in the experimental room every 12 h for about 1 h. All animals received a course of saline (NaCl 0.9%, 2 ml) injection (5 days) followed by 10 days of morphine injection, and then a further series of saline injection (7 days).

Before morphine administration, on five consecutive days, saline was injected every 12 h (days 1 to 5). During morphine administration, monkeys were treated by intramuscular injection of morphine–HCl twice per day at an interval of 12 h for 10 days (days 6 to 15). On the first day of morphine administration, the monkeys received 0.5 mg/kg morphine per injection. The dose was then daily increased to 1.6, 5.0 and 8.0 mg/kg on successive days. The highest dose of 8.0 mg/kg was maintained in the following 6 days. After 10 days of morphine administration, saline was injected instead of morphine for 7 days (days 16 to 22). Over experiments, the behaviors of monkeys were monitored continuously by a video camera.

2.4. Procedures for EEG recording and data analysis

Every morning of this experiment, EEG was recorded in the whole experimental sessions. After habituating the