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Phasic reward responses in the monkey striatum as detected by voltammetry with diamond microelectrodes

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ABSTRACT

Reward-induced burst firing of dopaminergic neurons has mainly been studied in the primate midbrain. Voltammetry allows high-speed detection of dopamine release in the projection area. Although voltammetry has revealed presynaptic modulation of dopamine release in the striatum, to date, reward-induced release in awakened brains has been recorded only in rodents. To make such recordings, it is possible to use conventional carbon fibres in monkey brains but the use of these fibres is limited by their physical fragility. In this study, constant-potential amperometry was applied to novel diamond microelectrodes for high-speed detection of dopamine. In primate brains during Pavlovian cue-reward trials, a sharp response to a reward cue was detected in the caudate of Japanese monkeys. Overall, this method allows measurements of monoamine release in specific target areas of large brains, the findings from which will expand the knowledge of reward responses obtained by unit recordings.

1. Introduction

Midbrain dopaminergic neurons are thought to transmit reward and reward-prediction signals to forebrain areas. Transient, sharply time-locked burst responses have been observed repeatedly in unit recordings of midbrain dopamine neurons (Fiorillo et al., 2003; Matsumoto and Hikosaka, 2009; Joshua et al., 2008; Takikawa et al., 2004; Schultz et al., 1993, 1997; Schultz, 2007). However, whether the chemical transmission at dopaminergic terminals linearly reflects the number of impulses transmitted by midbrain dopamine neurons is not well understood. First, the release can be modulated by facilitation and depression, depending on the firing history (Abeliovich et al., 2000; Garris et al., 1999; Kita et al., 2007; Phillips et al., 2002; Yavich, 1996; Zhang et al., 2009). Second, several factors, e.g., psychostimulants and nicotine, modulate dopamine release at synaptic terminals (Schmitz et al., 2003).

Dopamine detection using fast-scan cyclic voltammetry (FSCV) on carbon fibres has been highly successful in the past decade because of their high sensitivity and fast temporal resolution (Hafizi et al., 1990; Heien et al., 2004; Marsden et al., 1988; Kawagoe et al., 1993; Bath et al., 2000). In this study, we sought to perform high-speed electrochemical detection of dopamine in the striatum of behaving monkeys. In an early investigation of direct electrochemical recording of dopamine in the primate brain (Lindsay et al., 1981), the sampling speed was of the order of minutes. Gerhardt et al. (1996) recorded dopamine release in the monkey striatum using chronoamperometry with a carbon fibre; however, the monkey was anaesthetized. Cragg et al. (2002) recorded phasic dopamine release in the striatum of marmosets, but in this study brain slices were used. Shon et al. (2010) recorded evoked dopamine release in the striatum of the pig whose brain is as large as those of the monkeys; however, the animal was also anaesthetized.

Abbreviations: AA, ascorbate; DA, dopamine; FSCV, fast-scan cyclic voltammetry; BDD, boron-doped diamond; MFB, medial forebrain bundle; MRI, magnetic resonance imaging; PBS, phosphate-buffered saline; DOPAC, 3,4-dihydroxyphenylacetic acid; SW, square-wave differential pulse-voltammetry.

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The carbon fibres used widely in rodents are easy to snap; special caution is required for their insertion into the brain (Phillips and Wightman, 2003). For implantation in large brains, such as those of monkeys, it is clear that the implantation of carbon fibre microelectrodes would be restricted not only by the dura mater, but also by fissures and the choroid plexus. Because tungsten needles are widely used for electrophysiological recording in deep parts of primate brains, tungsten can be used to make an electrochemical probe for monkey brains. Because the surface of tungsten is not suitable for electrochemical detection of dopamine, in this study, a tungsten needle (0.3-mm diameter) was covered with boron-doped diamond (BDD) for use as an electrochemical probe. In general, diamond electrodes have wide voltage windows, low background current and low adsorption (Einaga et al., 2004; Fujishima et al., 2005). Recently, growing evidence has suggested the potential use of BDD as an electrochemical sensor. Furthermore, we have already shown that a diamond microelectrode on thin tungsten wire can be used for *in vivo* dopamine detection in the anaesthetized mouse brain (Suzuki et al., 2007). Whereas pulse voltammetry was used in the former study, we noticed that our novel diamond microelectrode could detect low concentration of dopamine on constant-potential amperometry. Using this technology, we observed a sharp increase in electrochemical current in the monkey striatum following a reward-predicting cue.

2. Materials and methods

2.1. Animals

Two Japanese monkeys (*Macaca fuscata*, male, 10 and 6 kg) participated in the reward experiments. One further monkey (male, 10 kg) and three C57BL/6J mice (male, 4–6 months old, Charles River Laboratories, Yokohama, Japan) were used for *in vivo* measurement of dopamine release evoked by electrical stimulation. The procedures were in accordance with the Guidelines for Proper Conduct of Animal Experiments established by the Science Council of Japan, and all experiments were approved by the Ethics Review Committee for Animal Experimentation of Juntendo University School of Medicine. All possible efforts were made to minimize the number of animals used and their suffering.

2.2. Electrochemical probes

2.2.1. Diamond microelectrodes

Boron-doped diamond (BDD) was formed on the surface of tungsten needles (0.3 mm diameter, 30 mm long) as previously described (Suzuki et al., 2007), except that the thin tungsten filaments were replaced by needles, and the boron doping in the carbon source was increased to 5%, from 1% in the previous study. In short, a thin diamond layer was formed on sharp tungsten needles by placing the needles in plasma with vapour from acetone and trimethoxyborane. The shaft of the microelectrode was connected to a stainless tube, yielding a microelectrode of 150 mm in length. The elongated shaft was insulated with cashew resin (Cashew Co. Ltd., Tokyo, Japan), excluding 1 mm from the tip (Fig. 1A). The surface of the diamond was oxidized with +2.5 V in 0.1 N HCl. Oxidization of the diamond surface improved dopamine selectivity at relatively low potentials (Suzuki et al., 2007).

2.2.2. Carbon fibre microelectrodes

Carbon fibre microelectrodes (Fig. 1A) were prepared as previously described (Natori et al., 2009; Oyama et al., 2010). Individual carbon fibres (7 μm in diameter, HTA-7, Toyo-RENAX, Tokyo, Japan) were sealed in pulled glass capillary tubes with epoxy-resin, such that 300 μm of the carbon fibres protruded from the capillary tubes.

2.3. Chemicals

Chemical reagents, including dopamine HCl (DA), serotonin HCl (5-HT), noradrenaline (NA), 3,4d-dihydroxyphenylacetic acid (DOPAC), ascorbate and nomifensine maleate, were purchased from Sigma-Aldrich (St. Louis, MO, USA). The other special-grade reagents were purchased from WAKO (Tokyo, Japan). To stabilize the pH of the solution, our phosphate-buffered saline (PBS) was 0.9% NaCl buffered with 100 mM phosphate-buffer (pH 7.4). To prepare acidic (pH 7.2) and basic (pH 7.6) pH-shifted buffers, 72.8 μl of 1 N HCl or 60.4 μl of NaOH, respectively, were added to 10 ml of PBS.

2.4. Electrochemistry

Constant potential amperometry was performed with the diamond microelectrode using a commercial control/recording system

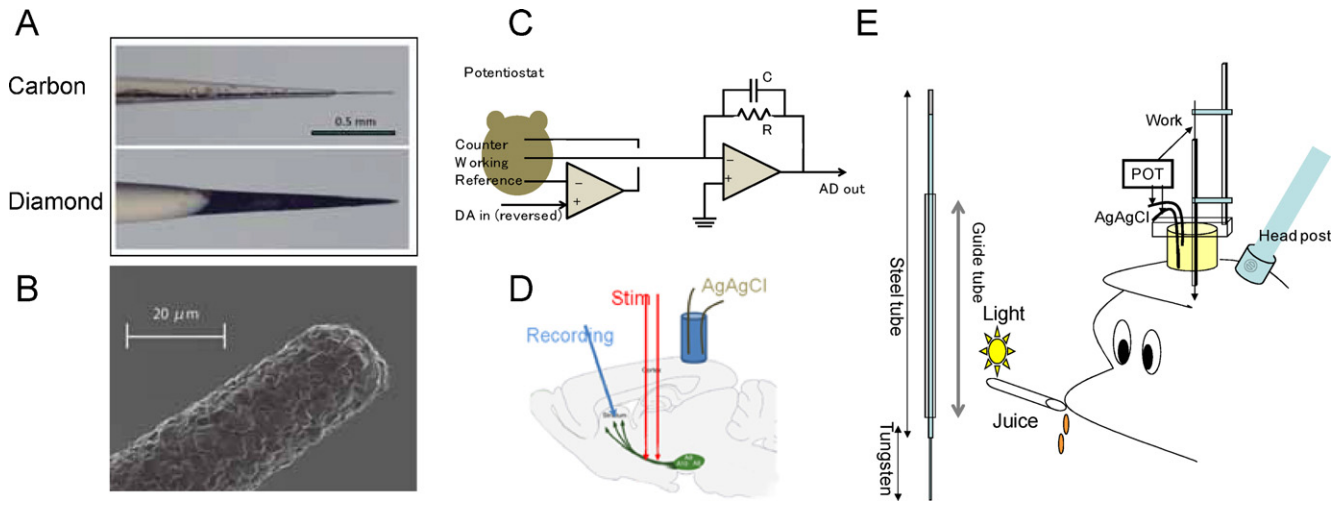

Fig. 1. Experimental methods. (A) Side view of the tips of carbon fibre (Cf) and diamond microelectrode (BDD). Scale bar = 500 μm. (B) Scanning electron microgram of the tip of the diamond microelectrode. (C) Circuit of potentiostat. (D) Electrode positions for the recordings in mouse brains. (E) Left: elongated diamond microelectrode and guide cannula. Right: microelectrode positions on the monkey head. POT: potentiostat.