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BRAIN RESEARCH

Research Report

Brief dopaminergic stimulations produce transient physiological changes in prefrontal pyramidal neurons

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ABSTRACT

In response to food reward and other pertinent events, midbrain dopaminergic neurons fire short bursts of action potentials causing a phasic release of dopamine in the prefrontal cortex (rapid and transient increases in cortical dopamine concentration). Here we apply short (2 s) iontophoretic pulses of glutamate, GABA, dopamine and dopaminergic agonists locally, onto layer 5 pyramidal neurons in brain slices of the rat medial prefrontal cortex (PFC). Unlike glutamate and GABA, brief dopaminergic pulses had negligible effects on the resting membrane potential. However, dopamine altered action potential firing in an extremely rapid (<1 s) and transient (<5 min) manner, as every neuron returned to baseline in less than 5-min post-application. The physiological responses to dopamine differed markedly among individual neurons. Pyramidal neurons with a preponderance of D1-like receptor signaling respond to dopamine with a severe depression in action potential firing rate, while pyramidal neurons dominated by the D2 signaling pathway respond to dopamine with an instantaneous increase in spike production. Increasing levels of dopamine concentrations around the cell body resulted in a dose dependent response, which resembles an "inverted U curve" (Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF (2007) Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci 10:376-384), but this effect can easily be caused by an iontophoresis current artifact. Our present data imply that one population of PFC pyramidal neurons receiving direct synaptic contacts from midbrain dopaminergic neurons would stall during the 0.5 s of the phasic dopamine burst. The spillover dopamine, on the other hand, would act as a positive stimulator of cortical excitability (30% increase) to all D2-receptor carrying pyramidal cells, for the next 40 s.

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1. Introduction

Transient release of dopamine (DA) in the brain is thought to occur upon expected food reward following positive reinforcers such as juice, or any cue that predicts the availability of the reward (Schultz, 2002). As a result of the behaviorally relevant stimuli DA neurons exhibit a burst of activity, which constitutes a phasic component of DA release in the brain

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Abbreviations: PFC, Prefrontal cortex; DA, Dopamine; DAr, Dopamine receptors; AP, Action potential; ACSF, Artificial cerebrospinal fluid; GABA, Gamma aminobutyric acid

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(Ljungberg et al., 1992). This "phasic mode" of DA release is thought to be important for proper functions of the prefrontal cortex, PFC (Williams and Goldman-Rakic, 1995; Schultz, 1998; Heien and Wightman, 2006). Since it is technically impossible to precisely control dopamine release during elaborate experimental paradigms by simply shocking the midbrain (Lewis and O'Donnell, 2000), researchers have mimicked transient DA release by iontophoretic application of dopamine via glass pipettes inserted into the cortex of awake monkeys (Sesack and Bunney, 1989; Matsumura et al., 1990; Williams and Goldman-Rakic, 1995; Sawaguchi, 2001; Vijayraghavan et al., 2007).

Although these experiments highlight the importance of DA in PFC, the cellular mechanisms by which DA modulates PFC function, specifically in terms of its influence on single cell activity, remain largely unknown. Single unit recordings in awake, behaving animals are not ideally suited to analyze the cellular mechanisms of dopaminergic effects. It is still not clear if the observed DA-ergic modulations of neuronal firing rate were mediated through modulation of synaptic inputs (synaptic excitability), modulation of neuronal membrane excitability (intrinsic excitability), or both. Additionally, continuous applications of exogenous dopaminergic drugs (≥ 60 s) (Vijayraghavan et al., 2007) cannot mimic the phasic dopamine activity that lasts shorter than 1 s (Ljungberg et al., 1992).

Here, we performed whole-cell measurements in rat PFC brain slices to determine the basic physiological effects of brief (phasic) DA release on layer 5 pyramidal neurons. The synaptic influences on neuronal membrane potential were silenced pharmacologically, allowing us to focus solely on intrinsic membrane properties. Dopaminergic drugs were delivered locally on the cell body for 2 s. By using a local drug release, we avoided the confounding influence of bath application of dopaminergic drugs reflected in the sustained, indiscriminant and simultaneous activation of all dopamine-responsive elements in the brain tissue. Miniature changes in membrane potential that arose from transient DA iontophoresis were evaluated, and compared with glutamate and GABA ejections, using identical experimental settings (i.e. stimulus current intensity, duration, shape of the drug pipette and its position and distance in respect to the cell body). Our data show the quality, quantity, and precise temporal dynamics of dopamine-induced changes on action potential output of a major projection neuron of the mammalian PFC, a layer 5 pyramidal cell. The observed transient changes in the neuronal action potential output may be occurring *in vivo* during behavioral paradigms that are characterized by phasic dopaminergic signaling, and also during *in vivo* experiments with microiontophoresis of dopamine (Vijayraghavan et al., 2007). A preliminary report has been presented in abstract form (Moore et al., 2009).

2. Results

2.1. *Neuron subtype*

Within the cortical layer 5, individual neurons were identified by their large pyramidal shaped cell body (~15 μm in diameter) and by the presence of long apical dendrites extending towards the pial surface (Milojkovic et al., 2005). In response to suprathreshold current steps these cells exhibited modest spike frequency accommodation, often after an initial spike doublet. This firing pattern corresponds to the "intrinsic bursting" cells described by Yang et al., 1996.

2.2. *Glutamate and GABA*

Local iontophoretic application of excitatory neurotransmitter glutamate (current intensity range: 20–100 nA) on layer 5 pyramidal neurons of the rat prefrontal cortex issued graded depolarizations of the membrane potential (Vr), as previously reported (Langomoen and Hablitz, 1981; Milojkovic et al., 2005). In each neuron tested with glutamate ($n=7$), the depolarization response was strong enough to elicit action potential firing followed by a depolarization block (Fig. 1B,

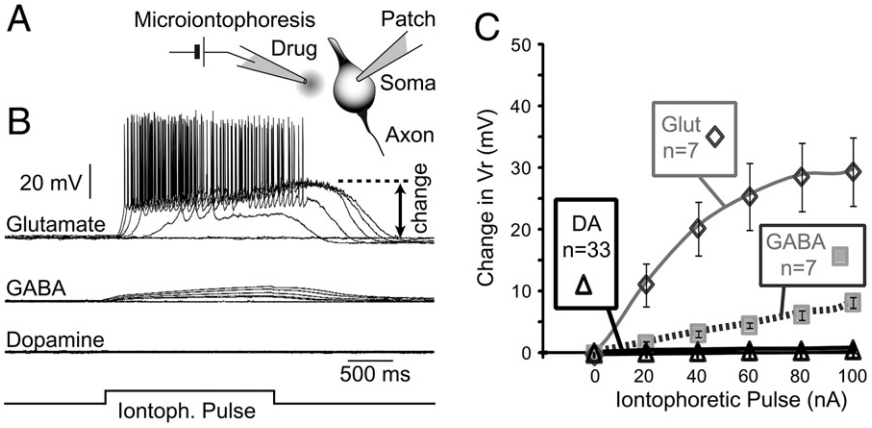

Fig. 1 – Local neurotransmitter application. (A) Schematic of the experimental paradigm in this and all the following figures. (B) Change in membrane potential (Vm) following glutamate, GABA, or dopamine iontophoretic application on layer 5 pyramidal neurons in the rat medial prefrontal cortex. In contrast to glutamate and GABA, dopamine has a negligible effect on resting voltage. Bottom trace marks the timing and duration (2 s) of the iontophoretic current pulse. (C) Average voltage response to glutamate (diamonds), GABA (squares), and dopamine (triangles) at different intensities of iontophoretic current, from 20 to 100 nA. *n*—indicates number of neurons per experimental group.

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