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Research report

Mechanism for optimization of signal-to-noise ratio of dopamine release based on short-term bidirectional plasticity

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ABSTRACT

Repeated electrical stimulation of dopamine (dopamine) fibers can cause variable effects on further dopamine release; sometimes there are short-term decreases while in other cases short-term increases have been reported. Previous studies have failed to discover what factors determine in which way dopamine neurons will respond to repeated stimulation. The aim of the present study was therefore to investigate what determines the direction and magnitude of this particular form of short-term plasticity. Fixed potential amperometry was used to measure dopamine release in the nucleus accumbens in response to two trains of electrical pulses administered to the ventral tegmental area of anesthetized mice. When the pulse trains were of equal magnitude we found that low magnitude stimulation was associated with short-term suppression and high magnitude stimulation with short-term facilitation of dopamine release. Secondly, we found that the magnitude of the second pulse train was critical for determining the sign of the plasticity (suppression or facilitation), while the magnitude of the first pulse train determined the extent to which the response to the second train was suppressed or facilitated. This form of bidirectional plasticity might provide a mechanism to enhance signal-to-noise ratio of dopamine neurotransmission.

1. Introduction

Dopamine release in the striatum is an essential feature of the neural networks responsible for motivational, cognitive and sensorimotor selections (Mink, 1996; Redgrave et al., 1999; Grillner et al., 2013). In particular, sensory evoked dopamine release is widely considered to provide the error signal necessary for driving reinforcement learning (Schultz et al., 1997; Da Cunha et al., 2012, 2009; Redgrave et al., 2010). Malfunctioning of dopamine neurotransmission has been implicated in several neurological diseases and psychiatric disorders, including Parkinson's disease (Hirsch et al., 2013), schizophrenia (Karam et al., 2010), drug abuse (Ikemoto, 2007), and attention deficit hyperactivity disorder (ADHD) (del Campo et al., 2011). With variable success, such conditions are typically treated either with dopaminergic drugs or by deep brain stimulation (DBS) of structures that are under the influence of dopamine (Da Cunha et al., 2015). To improve or further refine these therapeutic interventions, it will be necessary to gain a better understanding of the mechanisms that govern the release of dopamine, both in normal and pathological conditions.

Recent electrochemistry studies that measured the release of dopamine have reported that repeated electrical stimulation of dopamine fibers has variable effects on dopamine release. Sometimes the stimulation produced a short-term decrease of further dopamine release while at other times a short-term increase in dopamine release was reported (Kita et al., 2007; Montague et al., 2004; Cragg, 2003; Chadchankar and Yavich, 2011). This bidirectional short-term plasticity is considered paradoxical (Kita et al., 2007) and is subject to complex regulatory events involving Ca2+(Cragg, 2003), dopamine autoreceptors (Chadchankar and Yavich, 2011; Kita et al., 2007), density of dopamine transporters (DAT) (Chadchankar and Yavich, 2011), and indirect effects involving cholinergic, glutamatergic, GABAergic, cannabinoid, and opioid receptors in the striatal micro-circuitry (Rice et al., 2011). These

Abbreviations: DBS, deep brain stimulation; NAc, nucleus accumbens; VTA, ventral tegmental area; ADHD, attention deficit and hyperactivity disorder.

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influences can vary according to the striatal sub-area where the release of dopamine was measured, the location and pattern of the electrical stimulation, and the immediately preceding activity of the dopamine fibers (see Rice et al. (2011) for a review).

The purpose of the present study was therefore two fold. First, by systematically varying the magnitude of the electrical stimulation over a wide range we sought to establish the conditions under which short-term facilitation or short-term suppression of dopamine release is observed. Consequently, when the two pulse trains were of equal magnitude we found that low magnitude stimulation was associated with short-term suppression and high magnitude stimulation with short-term facilitation. Secondly, we investigated the role of each of the two stimulating pulse trains in dopamine short-term plasticity. We found that the magnitude of the second pulse train was critical for determining the sign of the plasticity (suppression or facilitation), while the magnitude of the first pulse train determined extent to which the response to the second train was suppressed or facilitated. These data suggest that the release of dopamine in response to electrically stimulating pulse trains is controlled in a manner that optimizes the signal-to-noise ratio of dopamine neurotransmission.

2. Results

Histological analysis confirmed that the stimulating and recording electrodes were located respectively among dopamine cell-bodies in the VTA and in the dopamine terminal regions of the NAc (Fig. 1). The anatomical specificity of our stimulation protocol was confirmed by the failure of electrical stimulation (40 pulses, 800 μA, 50 Hz) at a site 0.3 mm dorsal to the VTA (Fig. 2A) to evoke dopamine release into the NAc (Fig. 2B). Identical stimulation of the VTA was effective (Fig. 2B).

In the first series of experiments, when stimulating the VTA with pairs of identical pulse trains, we observed both short-term decreases and increases in dopamine release evoked by the second pulse train (Fig. 3). By varying both the number of pulses (Fig. 3A) or the intensity of the stimulating pulse trains (Fig. 3B), we showed that the short-term difference between the amount of dopamine evoked by S1 and S2 was critically dependent on the overall level of dopamine evoked by the stimuli. If the amount of released dopamine was small, the second peak of dopamine (P2) was reduced below that of the first peak (P1) (Fig. 3A and B). Conversely, if the amount of released dopamine was large, then S2 typically evoked a larger dopamine release (P2) compared with P1 (Fig. 3A and B). Differences between the average amounts of dopamine released by S1 and S2 were statistically reliable [Fig. 3B; $F(4,27) = 134$, $p < 0.001$, one-way ANOVA]. The differences between the concentrations of dopamine release at P2 and P1 were negative (short-term suppression) when the applied currents were low (≤600 μA), and positive (short-term facilitation) when the applied current was large (800 μA) (Fig. 3C). Correlations between DA concentration at P2 and the difference between P2 and P1 were significant when the applied currents were 400 μA, 600 μA or 800 μA ($P < 0.001$, Pearson's test). When the current was 200μA the correlation between these variables was marginally insignificant

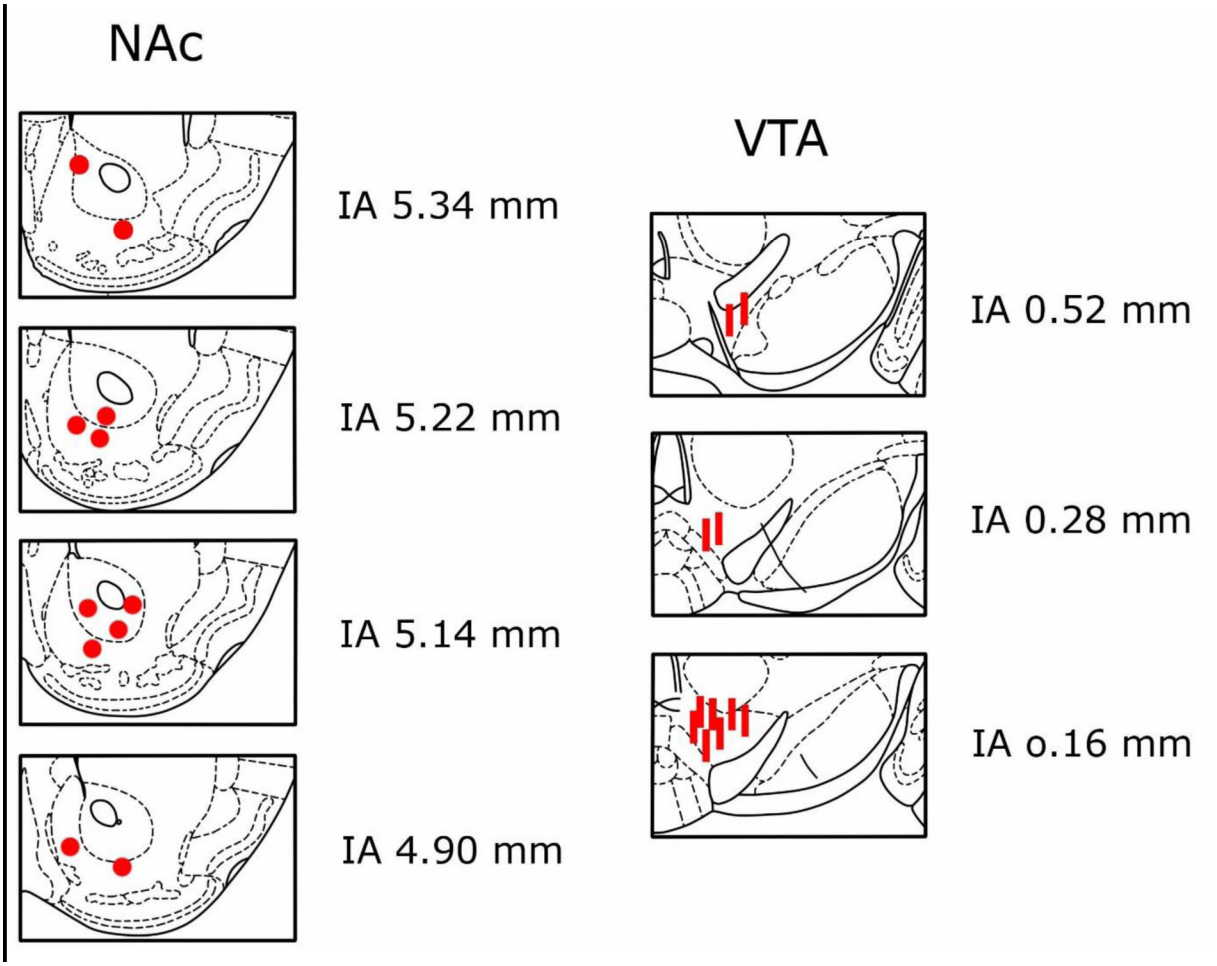

Fig. 1. VTA stimulation sites and NAc recording sites are indicated by red marks. Numbers to the right of individual sections show distance in mm from inter-aural line. Sections were adapted from the atlas of Paxinos and Franklin (2007).