ELECTRICAL STIMULATION USES SODIUM CHANNEL DEPENDENT DEPOLARIZATION TO PRODUCE EXOCYTOTIC-LIKE DOPAMINE RELEASE AND ROTATIONAL BEHAVIOR *IN VIVO*

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Dedicated to Baby G, the most important person in my life that I have not met

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Abstract

The goal of this project was to establish Electrical Stimulation (ES) in combination with *In Vivo* Intracerebral Microdialysis (IVMCD) as a methodology to evoke exocytotic-like dopamine (DA) release. To provide evidence that ES mimics action potential-mediated DA exocytosis, we hypothesized that ES produces depolarization of the membrane potential that is dependent upon sodium (Na^+) -channels to produce DA release concomitantly with rotational behavior. To test this, rats received electrode and cannulae implants along the medial forebrain bundle, which contains the DAergic nigrostriatal pathway, and a microdialysis probe at the striatum to undergo IVMCD testing. To begin, steady baseline DA levels were assessed followed by ES, subsequent post ES samples were collected, followed by an infusion of Na^+ channel blocker, lidocaine. Next, a second phase of ES was applied to assess the effects of lidocaine on ES-evoked DA overflow, and two additional post ES samples followed. The data indicate that lidocaine decreased both basal and electrically stimulated DA release, and reduced associated rotational behavior. The current data support the idea that ES activates Na^+ channels to induce exocytotic-like DA release and rotational behavior. These data validate ES in combination with IVMCD as an effective methodology to study plasticity of exocytotic mechanisms that alter DA neurotransmission. Specifically, future research that aims to understand how DA neurotransmission is altered in behavioral disorders, such as neurodegenerative or substance use disorders, can utilize this innovative combination of ES and IVMCD.

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Introduction

History of Electrical Stimulation

Electrical stimulation (ES) has played an important role in elucidating how electrical currents are important in the physiological function of neurons as well as the functional organization of the nervous system. The role of electricity in biological systems was formally investigated for the first time in the 18th century when Luigi Galvani discovered that muscle movements could be evoked when applying electrical current to muscle tissue of the Peripheral Nervous System (Piccolino, 1997). This discovery helped to conceptualize that a cell has the capability to generate its own electrical energy. It was not until the late 19th century when Fritsch and Hitzig revealed that the Central Nervous System was electrically excitable. Using ES, they discovered that the cortex was important for producing behavior, and that different behaviors were localized in different locations of the cortex (Fritsch & Hitzig, 1870).

ES has been a valuable tool to map other brain functions beyond the initial findings by Fritsch and Hitzig. For example, a topographical representation of the cortex was developed based on electrically evoked sensory and motor behavior (Penfield & Jasper, 1955; Woolsey, 1979). ES of the lateral hypothalamus has also been shown to evoke motivated feeding behavior (Hoebel & Teitelbaum, 1962; Berridge & Valenstein, 1991) and to discover that other limbic structures, such as the septal nucleus, modulate reinforcement (Olds & Milner, 1954). Therefore, ES of brain circuits has been an important tool in neuroscience to elucidate the behavioral organization of the Central Nervous System.

Thus, ES has been used to explore functional circuits by correlating evoked behaviors with stimulated brain sites. Moreover, the ability to study the effects of ES at the neuronal level