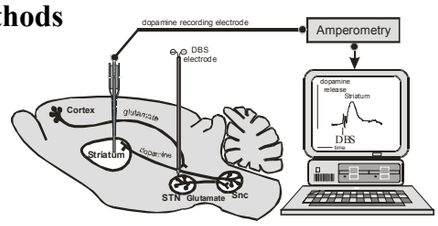
STN HIGH FREQUENCY STIMULATION RESULTS IN STN GLUTAMATE RELEASE AND STRIATAL DOPAMINE RELEASE IN THE RAT: POTENTIAL MECHANISM OF ACTION IN PARKINSON'S DISEASE

Kendall H. Lee, M.D., Ph.D., Charles Blaha, Ph.D., Katarina J. Kristic, Frederick L. Hitti, C. Daniel Ansevin, M.D., Chris Muly, M.D., Ph.D., Brent Harris, M.D., Ph.D., J.C. Leiter, M.D., and David W. Roberts, M.D.

Introduction

It has been previously shown that subthalamic nucleus (STN) high frequency stimulation (HFS) results in neurotransmitter release. In the present study, we investigated the hypothesis that, with STN HFS, the specific neurotransmitters dopamine and glutamate are released in the striatum and the STN, respectively.

Methods

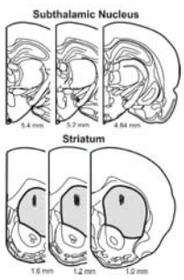


Constant potential dopamine amperometry was performed in the striatum using carbon fiber microelectrodes. Measurement of glutamate release in the STN was made using a dual enzyme-based electrochemical sensor in the anesthetized rat placed in a stereotactic head frame. Electrical stimulation using a bipolar stimulating electrode was delivered to the STN or the area immediately dorsal to STN. Dopaminergic fibers were labeled using monoclonal antibody to tyrosine hydroxylase (TH) or dopamine transporter (DAT) in rat, ferret, monkey, and human brains to examine the anatomical localization of catecholaminergic pathways in relation to the STN.

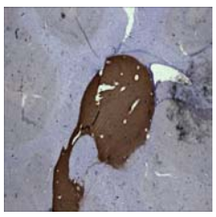
Results

1

Electrode placement

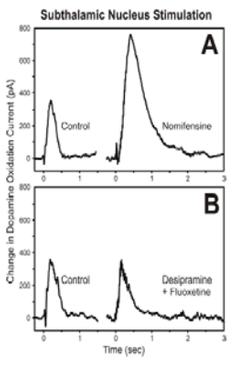


Caudate DAT stain

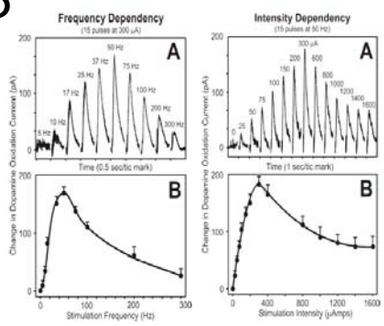


2

Stimulation of the STN resulted in striatal dopamine release that is increase by DAT inhibitor nomifensine but not by desipramine or fluoxetine (NE and 5-HT reuptake inhibitors).



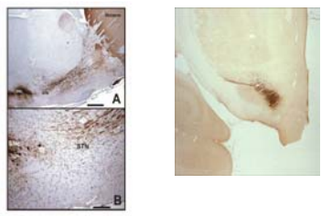
3



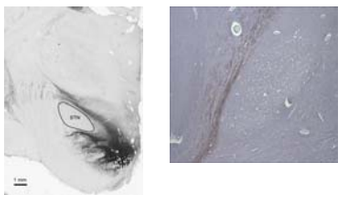
Frequency and intensity dependency of striatal dopamine release with STN HFS.

4

Rat (TH stain) Ferret (DAT stain)

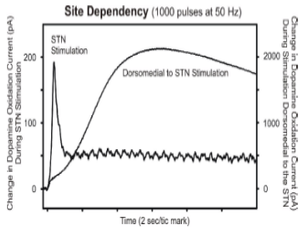


Monkey (TH stain) Human (TH stain)



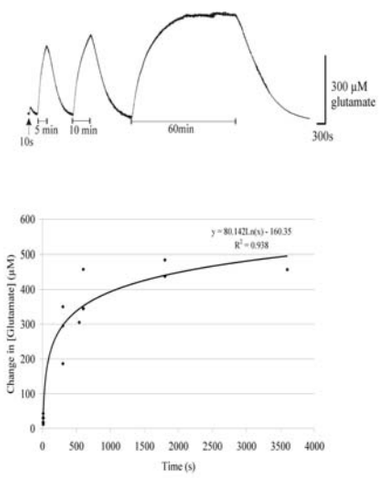
Antibody staining demonstrate dopaminergic axons running dorsal to STN.

5



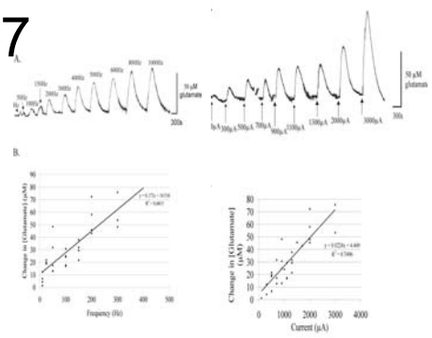
Striatal dopamine levels returned to near pre-stimulation levels within 1 sec despite the continued application of electrical stimulation to STN. In contrast, similar stimulation of the area just dorsal to the STN resulted in greater striatal dopamine release that was sustained over the course of the stimulation.

6



STN glutamate levels remained elevated for the duration of stimulation.

7



Frequency and intensity dependency of STN glutamate release with STN HFS.

Conclusions

STN HFS increases glutamate release in the STN and dopamine release in the striatum. Stimulation dorsal to the STN caused greater dopamine release than did stimulation within the STN. The presence of dopaminergic fibers immediately dorsal to the STN raises the possibility that these dopaminergic fibers may be stimulated directly to release striatal dopamine. Thus, enhanced neurotransmitter release may be an important mechanism whereby HFS of the STN improves the symptoms of Parkinson's Disease.

Reference

Lee KH, Chang SY, Roberts DW, Kim U (2004) Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. J Neurosurg 101:511-517.