Stereotact Funct Neurosurg 2008;86:216–218
DOI: [10.1159/000131658](https://doi.org/10.1159/000131658)

Activation of Subthalamic Nucleus Outflow by High-Frequency Stimulation Is Consistent with the Nigral Control of Epilepsy Model

Robert E. Gross

Department of Neurosurgery, Center for Neurodegenerative Diseases, Emory University School of Medicine Atlanta, Ga., USA

Zhang et al. [1] examined the effects of two levels of high-frequency stimulation of the subthalamic nucleus (STN) on the concentration of extracellular glutamate and γ -aminobutyric acid (GABA) in the globus pallidus (GP) and substantia nigra pars reticulata (SNr) of normal or kainate-induced spontaneously epileptic adult rats. They interpret their results in terms of the mechanism of antiepileptic properties of STN stimulation.

This study is focused on an important question, namely the actual mechanisms of action at play during electrical stimulation within the so-called nigral control of epilepsy circuit first elucidated by Karen Gale and colleagues [2, 3] in the 1980s and subsequently by others including the Grenoble group of Deransart et al. [4]. The essential insight of Gale's group was that bilaterally inhibiting the SNr (with the GABA agonist muscimol) blocked limbic seizures – induced by injection of the GABA antagonist bicuculline into the self-named *area tempestas* ('tempest' = 'gale') – as well as other types of seizures [5, 6]. It is thought that the mechanism of this nigral control of epilepsy circuit proceeds through decreased activity of the inhibitory projection of the SNr to the deep layers of the superior colliculus which upregulates a widespread projection to cortical regions (fig. 1a, b). The French group [7] extended these findings by using high-frequency stimulation (HFS) of the STN with the notion that this would inhibit the glutamatergic drive on the SNr and provide a more therapeutically practical way of decreasing SNr activity – the prevailing notion at the time being that STN HFS is inhibitory of its output. Electrical stimulation of the SNr was not considered because of its large size. Indeed, STN HFS was shown in various models including the absence rat to be effective, providing the rationale for two small pilot studies [8, 9] with mixed but in part promising results leading to an ongoing large clinical trial in France of STN deep brain stimulation for ring chromosome syndromic epilepsy. The problem is: the weight of the evidence [10] is that STN HFS actually *drives* its axonal projections (at a regular rate) rather than inhibiting them [11, 12]. So: what is STN HFS *really doing* that controls epilepsy in these animal and human studies?

Zhang et al. [1] found that STN HFS at 130 Hz (the most popular frequency for HFS) for 1 h increased glutamate concentrations in the GP and SNr, which were maximal 1 h after stimulation, but still very elevated at 2 h. In contrast, HFS at 130 Hz (or 260 Hz) had absolutely no effect on GABA levels in the GP. However, both conditions led to substantial and sustained increases in GABA (with a similar time course to glutamate levels) in the SNr. In epileptic rats, baseline GABA levels were increased in the SNr (but not GP) and the GABA-inducing effects of STN HFS were greater than in normal rats. Finally, STN HFS at 260 Hz also markedly elevated SNr and GP glutamate levels (in normal and epileptic rats) with a similar time course but to a slightly lesser degree compared to 130 Hz, whereas the GABA-elevating effects in the SNr were slightly greater at 260 Hz than 130 Hz.

How should these data be interpreted? First, it should be remembered that the GP in the rat is equivalent to the external segment of the GP (GPe) in primates, not the internal segment, which in rats is the entopeduncular nucleus [to emphasize this I will denote the GP of the rat as 'GP(e)']. The glutamate-elevating effects of STN HFS in the SNr and GP(e) are consistent with an *activation* of STN by HFS, with the SNr receiving the glutamatergic fibers of the STN, and the GP(e) receiving recurrent glutamatergic STN fibers (fig. 1c) [13, 14]. This stands in contrast to the notion behind the initial experiments on epileptic rats where it was thought a priori that STN HFS would inhibit its output. But does this glutamate elevation in the SNr drive an increase in its output? The finding that GABA is elevated as well in the SNr is critical and unexpected. This would result in overall inhibition of the SNr, despite an STN-mediated increase in glutamate release, since GABA receptors are located more proximally on cell soma thus negating excitation elicited by glutamate receptors located more distally on dendrites. As a result, nigral projections will likely be inhibited leading to increased antiepileptic outflow from the superior colliculus, consistent with the clinical results of STN HFS and the nigral control of epilepsy model. The observation of decreased metabolic activity [15] and firing rate [16] in the SNr with STN HFS is consistent with this prediction.

By what mechanism might GABA levels be increased in the SNr by STN HFS? The SNr receives GABA afferents from the striatum (direct pathway), but also the GP(e) (indirect pathway) [17]. Thus, elevation of GABA in the SNr might result from the activation of pallidal-nigral efferents by recurrent STN-GP(e) glutamatergic fibers, consistent with the increased glutamate levels in the GP(e) found in this study. Other explanations may exist as well. However, antidromic activation of corticostriatal efferents (via the monosynaptic cortico-STN projection) is unlikely since this would be expected to lead to elevation of GABA in the GP(e) (via

Fig. 1. The circuitry through the basal ganglia projecting to the deep layers of the superior colliculus are illustrated. GP(e) = Globus pallidus (equivalent to external GP in primates); Sup Coll = superior colliculus; Glu = glutamate. **a** Projections in untreated animals, with excitatory (glutamatergic) ones depicted with an arrow and inhibitory (GABAergic) ones depicted with a circle. **b** The results of Gale et al. [2] in which muscimol injection into the SNr inhibits its output, thus disinhibiting the antiepileptic

projections from the superior colliculus. **c** The results of Zhang et al. [1] in which STN HFS drives its glutamatergic outflow to both the GP(e) and SNr. However, the resulting GP(e) activation inhibits the SNr. Since inhibitory GABA receptors act more proximally to excitatory glutamate receptors, the net effect is to inhibit SNr output resulting in antiepileptic disinhibition of the superior collicular projections.

GABAergic striatopallidal neurons) – which was not observed in this study – in addition to GABA elevation in the SNr.

It is hard to know how meaningful the results with 260-Hz stimulation are because this frequency of stimulation has not been studied for its antiepileptic (or movement) effects. However, the increased GABA levels in the SNr, combined with the decreased glutamate levels, predict that this frequency of stimulation will have greater inhibitory effects on SNr output. Thus, we look forward to seeing the effects of 260-Hz STN HFS on seizure frequency in this model and others.

This study is an example of how actually examining the downstream effects of electrical brain stimulation in clinically relevant animal models (as well as normal animals) can provide insight into the mechanisms of action, and lead to refinement of therapies that may lead to increased clinical effectiveness. Then, rather than encoding negative clinical trial results as failures and prematurely abandoning them, they can be optimized based on these insights and reincarnated. A cogent argument can be made that these types of experiments should be performed *before* the human clinical trials, but the fact that patients are undertreated by extant therapeutics provides some rationale (in addition to the drive to get to the market first with a new therapy) for early clinical pilot experiments. The important point is not to let negative results from prematurely introduced treatments put a damper on future iterations resulting from translation of basic animal experiments such as those of Zhang et al. [1] into therapy improvements.

References

- 1 Zhang B, Chu J, Zhang J, Ma Y: Change of extracellular glutamate and gamma-aminobutyric acid in substantia nigra and globus pallidus during electrical stimulation of subthalamic nucleus in epileptic rats. *Stereotact Funct Neurosurg* 2008;86:208–215.
- 2 Iadarola MJ, Gale K: Substantia nigra: site of anticonvulsant activity mediated by gamma-aminobutyric acid. *Science* 1982;218:1237–1240.
- 3 Garant DS, Gale K: Lesions of substantia nigra protect against experimentally induced seizures. *Brain Res* 1983;273:156–161.
- 4 Deransart C, Marescaux C, Depaulis A: Involvement of nigral glutamatergic inputs in the control of seizures in a genetic model of absence epilepsy in the rat. *Neuroscience* 1996;71:721–728.
- 5 Piredda S, Gale K: A crucial epileptogenic site in the deep prepiriform cortex. *Nature* 1985;317:623–625.
- 6 Garant D, Gale K: Intrastriatal muscimol attenuates electrographic signs of seizure activity induced by intravenous bicuculline in rats. *Eur J Pharmacol* 1986;124:365–369.
- 7 Vercueil L, Benazzouz A, Deransart C, Bressand K, Marescaux C, Depaulis A, Benabid AL: High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. *Epilepsy Res* 1998;31:39–46.
- 8 Chabardes S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL: Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. *Epileptic Disord* 2002;4(suppl 3):S83–S93.
- 9 Dinner DS, Neme S, Nair D, Montgomery EB Jr, Baker KB, Rezaei A, Luders HO: EEG and evoked potential recording from the subthalamic nucleus for deep brain stimulation of intractable epilepsy. *Clin Neurophysiol* 2002;113:1391–1402.
- 10 Perlmuter JS, Mink JW: Deep brain stimulation. *Annu Rev Neurosci* 2006;29:229–257.
- 11 Hahn PJ, Russo GS, Hashimoto T, Miocinovic S, Xu W, McIntyre CC, Vitek JL: Pallidal burst activity during therapeutic deep brain stimulation. *Exp Neurol* 2008, in press.

- 12 Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL: Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J Neurosci* 2003;23:1916–1923.
- 13 Van der Kooy D, Hattori T: Single subthalamic nucleus neurons project to both the globus pallidus and substantia nigra in rat. *J Comp Neurol* 1980;192:751–768.
- 14 Delfs JM, Ciaramitaro VM, Parry TJ, Chesselet MF: Subthalamic nucleus lesions: widespread effects on changes in gene expression induced by nigrostriatal dopamine depletion in rats. *J Neurosci* 1995;15:6562–6575.
- 15 Benazzouz A, Tai CH, Meissner W, Bioulac B, Bezard E, Gross C: High-frequency stimulation of both zona incerta and subthalamic nucleus induces a similar normalization of basal ganglia metabolic activity in experimental parkinsonism. *FASEB J* 2004;18:528–530.
- 16 Tai CH, Boraud T, Bezard E, Bioulac B, Gross C, Benazzouz A: Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridges neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. *FASEB J* 2003;17:1820–1830.
- 17 Kita H, Kitai ST: The morphology of globus pallidus projection neurons in the rat: an intracellular staining study. *Brain Res* 1994;636:308–319.

Robert E. Gross, MD, PhD
Department of Neurosurgery, Center for Neurodegenerative Diseases
Emory University School of Medicine
Atlanta, GA 30322 (USA)
Tel. +1 404 727 2354, Fax +1 404 778 4472
E-Mail robert.gross@emoryhealthcare.org