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The Pedunculo pontine Tegmental Nucleus: from Basic Neuroscience to Neurosurgical Applications Commentary:

The Pedunculo pontine Nucleus: Clinical Experience, Basic Questions and Future Directions

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Abstract

This issue is dedicated to a potential new target for the treatment of movement disorders, the pedunculo pontine tegmental nucleus (PPTg), or, more simply, the pedunculo pontine nucleus, that some authors abbreviate as PPN. We provide an overview of the field as an introduction to the general reader, beginning with the Clinical Experience to date of Mazzone and co-workers in Rome, some Basic Questions that need to be addressed, and potential Future Directions required in order to ensure that the potential benefits of this work are realized.

2. Clinical Experience

The first clinical experience for deep brain stimulation (DBS) of the PPTg in Parkinson's Disease (PD) was carried out on February 1st 2005, at the Functional and Stereotactic Neurosurgery Unit of the CTO Hospital in Rome in a parkinsonian patient who, during the same surgical session, was also implanted in the subthalamic nucleus (STN) in the same hemisphere. The rationale for choosing the PPTg as a novel target for DBS grew from a large amount of experimental data and anatomical considerations concerning the input-output connections of the PPTg, largely discussed in some chapters of this issue. We focused on parkinsonian patients who presented severe axial symptoms and gait disorders not responsive to L-Dopa treatment. At that time, we used traditional stereotactic approaches for targeting the PPTg, based on ventriculography, and supported by intraoperative neurophysiological recordings. Before placing the stimulating lead, we attempted to explore the spontaneous electrical activity of putative PPTg neurons. The intraoperative microrecording was not followed in the first patient by implantation of a stimulating lead in the PPTg for reasons of safety since no reference data existed at that time in the literature concerning the exact location of the target and the effects of PPTg stimulation in the human, thus only the STN was implanted. The gradual development of the surgical methods for implanting the PPTg was completed in the successive two patients, who were implanted in

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the PPTg using a Medtronic 3389 lead. After surgery, stimulation of the PPTg was carefully performed with patients initially in the supine position to ascertain possible side effects of PPTg DBS on cardiovascular and respiratory functions. The data obtained in these three patients were presented at the World Society for Stereotactic and Functional Neurosurgery Meeting held in Rome in June 2005 (Mazzone et al. 2005a). The first patients were implanted in both the PPTg and STN in the same hemisphere in one surgical session, and 10–15 days later in both nuclei in the opposite hemisphere (Mazzone et al. 2005b). Five out of the first 6 patients were operated with the aid of traditional mapping methods, i.e. ventriculography and indirect targeting (Stefani et al. 2007). In the subsequent 18 patients the targeting technique was refined, and patients underwent a direct targeting method based on Angio-CT scans and tridimensional reconstruction of nuclei and cerebral vessels (Mazzone et al. 2008; Mazzone et al. 2009). The novel methodology and the employment of well encoded extraventricular, intrapeduncular and translemniscal trajectories allowed us to avoid complications related to the surgical approach. This procedure also permitted us to standardize the target coordinates and the reproducibility of the technique, as demonstrated by postoperative MRI or CT scan controls performed in all patients.

The direct neuroradiological verification that we used permits real time control of lead positioning, and appears to be more reliable with respect to the representation of nuclei that can be obtained from neurosurgical brain atlases currently employed. Moreover, the procedure of implanting different targets in separate sessions permits a mathematical comparison between the planned and the realized coordinates. During the course of our experience, we modified the traditional approach for implanting basal ganglia nuclei such as the STN. Furthermore, in the last several years we also modified the intraoperative management of patients and refined neurophysiological investigations. Recordings of neuronal activity were discontinued after the first six patients since they did not reveal consistent data useful for localizing the PPTg, and also to avoid the risks inherent in the penetration of microelectrodes. Rather, the recording of Somato Sensory Evoked Potentials (SSEPs) proved to be of great intraoperative value for driving surgery while, postoperatively, the study of the Blink Reflex helped to ascertain the exact site of the contact lead in the PPTg. It is noteworthy that the procedures for exploring these parameters, contrary to intraoperative microrecordings, are devoid of risks, and the recording of SSEPs may be performed under general anesthesia. The use of general anesthesia is extremely helpful when dealing with the psychological well-being of patients, and saves time during the surgical procedure. Together with the classic subjective clinical evaluation scales (UPDRS), we decided to collect objective evaluations of movement through kinematic analysis of gait and oromandibular movements, and surface EMG recordings during postural tasks. These techniques allow us to collect consistent and quantifiable data without introducing subjective variables, for example, on UPDRS scores. Moreover, before and after surgery as well as in follow-up controls, the patients' clinical conditions were video recorded in the on and off state, on and off drugs, and under double-blind condition. All of the treated patients showed improvements in walking, postural stability and oromandibular movements. Since 2007, we reduced the number of implanted leads, and consequently, we could verify that even a single PPTg lead was sufficient to improve parkinsonian symptoms, thus mimicking the effects of a single implantation of the STN (Walker et al. 2009). The procedure of a monolateral implantation of the PPTg has been also adopted by other authors (Strafella et al. 2008; Weinberger et al. 2008; Moro et al. 2010).

Given the above results, our preferred strategy is based on a unilateral implantation of the PPTg which, in selected patients, appears to be effective not only on axial and gait symptoms, but also on the majority of non axial parkinsonian symptoms. The pharmacological treatment of these patients usually needed to be modulated, in general involving a reduction of drug dosage. In some patients who showed fluctuating responses to

subcutaneous apomorphine or lisuride and inconsistent responses to oral drugs, the therapy could be discontinued, with some requiring no further treatment while remaining clinically stable. Another important finding that arises from the study of these patients was the consistency of the clinical effect of PPTg DBS. In fact, three patients who had the stimulating lead removed, when reimplanted in the PPTg, showed the same clinical results as following the first implantation. The encouraging results obtained in the overall number of our patients (a total of 23 to date) support the clinical value of the PPTg as a primary target of choice for treating PD selected patients affected by severe gait and postural disorders, and who are unresponsive to pharmacological therapy.

Other groups, in previous reports (Moro et al. 2010; Ferraye et al. 2010) as well as in this issue, have reported different results, i.e. benefits on decreasing falls but no significant improvements in gait and /or in other symptoms. It is likely that the discrepancies between their data and our most recent results, may be due to differences in the surgical approach and/or selection of patients, as well as to differences in the site of stimulation (Piallat et al. 2009). Unfortunately, some authors continue to make reference to our first 6 patients without considering the evolution of our surgical approach for the correct targeting of the PPTg. Rather, they seem to give preference to the STN as the choice structure for surgical treatment of PD. Undoubtedly, a changing role of the STN in the traditional approach of Functional Neurosurgery can not be denied, but perseveration in this conservative view may limit the perspectives of DBS based on multiple implantations, that must be tailored on the basis of motor disabilities presented by each patient, and not on general rules.

According to the above considerations, in our opinion the best neurosurgical strategy for a tailored DBS in patients eligible for PPTg implantation should consist initially of implanting the PPTg, and only successively, if required, other classic targets (Mazzone et al.; 2003, Mazzone et al. 2006; Mazzone and Scarnati 2009; Mazzone et al. 2009).

3. Basic Questions

3.1 PPTg and spinal efferents

Experimental data show that PPTg neurons are scattered over a large pontotegmental region which, when stimulated, modulates spinal motoneuronal excitability. This is of great value since the improvement of rigidity observed during PPTg-DBS in PD may be ascribed not only to stimulation of PPTg neurons but also to activation of descending fibers running in the region in which PPTg neurons send axons to reticulospinal systems.

Many important aspects of the the relationships between PPTg neurons, spinal motoneurons and interneurons remain to be investigated. For example, it is not known to what extent PPTg fibers: 1) innervate alpha and gamma motoneurons as well as spinal interneurons, 2) what sort of influence they exert on these elements, and 3) whether they modulate Ia, Ib and II afferents, and spinal cord interneurons responsible for reciprocal and non-reciprocal inhibition. If PPTg neurons activate reticulospinal neurons that are inhibitory to motoneurons, we should expect a decrease in motoneuronal excitability. The contrary should occur if excitatory reticulospinal fibers are activated, or if PPTg descending fibers exert a direct excitatory influence that could counterbalance inhibitory reticulospinal activity. Clarification of the above issue may help us understand the role of PPTg neurons in muscle tone and rigidity, and optimize stimulation parameters for DBS in the pontine tegmentum.

Since the PPTg is part of the mesencephalic locomotor region, the effect of PPTg DBS on locomotion and posture might arise through the modulation of spinal pattern generators, as well as through modulation of spinal mechanism whose disruption in PD contributes to rigidity. It should be noted that a body of work from the Oxford group was instrumental in

developing the PPN as a target for DBS in the human. These studies included testing of the effects of stimulation of the PPN in nonhuman primates (Jenkinson et al. 2004), performing lesions of the PPN in these animals (Munro-Davies et al. 2001), and making injections into the PPN in such primates (Nandi et al. 2002). For a review, see Nandi et al. 2008.

3.2 Stimulation Technique

3.2.1 Duration—An important consideration when selecting stimulus parameters for DBS is pulse duration. When stimulating nerve tissue, the rheobase is the lowest intensity that can activate the tissue, while the chronaxie is the pulse duration at which the threshold intensity is twice that of the rheobase (Irnich 1980). The chronaxie of fibers is lower than that of cells (Nowak and Bullier 1998), so that stimuli in the 50–100 μ sec range preferentially activate fibers, while durations of 400–1000 μ sec preferentially activate neurons. The parameters of stimulation used to induce locomotion in the decerebrate cat (Shik et al. 1966; Garcia-Rill 1986, 1991) or rat (Skinner and Garcia-Rill 1984) have always been in the 500–1000 μ sec range. A more recent study (Takakusaki et al. 2004) used a low-intermediate duration of 200 μ sec, which makes it difficult to ascribe effects on fibers vs cells. Moreover, this study used very low amplitude stimuli to induce locomotion, which suggests that fibers of passage were likely the most activated tissue components. This sheds doubts on the results reported. Current practice in DBS is to stimulate using 50–100 μ sec pulses, which may preferentially be activating intrinsic axons and fibers of passage rather than neurons.

3.2.2 Frequency—The optimal frequency of stimulation in order to induce locomotion in the decerebrate cat (Shik et al. 1966; Garcia-Rill 1986, 1991) or rat (Skinner and Garcia-Rill 1984) has always been reported as 40–60 Hz. Frequencies lower than these were generally ineffective, while frequencies in the 100–300 Hz range induced changes in muscle tone (Lai and Siegel 1991). Recent evidence for cells in the PPTg shows that, when these cells are maximally activated, whether by intracellular current steps, or by pharmacological agents, all PPTg cells, regardless of cell type, plateau at 40–60 Hz firing frequency (Simon et al. 2010). The chapter by Garcia-Rill et al shows that increasing amplitude current pulses lead to a rapid plateau in firing frequency in every cell type (Type I, II, or III) or transmitter type (cholinergic, glutamatergic or GABAergic). This may explain why locomotion-inducing frequencies had to reach 40–60 Hz in order to activate the PPTg. Higher frequencies of stimulation may tend to depolarize-block these neurons, leading to cessation of firing. Current practice in DBS is to use frequencies >100 Hz, which, when applied to PPTg, may actually tend to inactivate these neurons.

3.2.3 Latency of effects—Stimulation of locomotion-inducing sites in the midbrain have universally required several seconds of stimulation before the first step ensued (Shik et al. 1966; Garcia-Rill 1986, 1991; Skinner and Garcia-Rill 1984; Takakusaki et al. 2004). This prompted us to propose that locomotion is not induced, but rather recruited over a period of time (Garcia-Rill 1991; Garcia-Rill and Skinner 1991; Reese et al 1995). Therefore, the practice of applying continuous DBS throughout the day may not result in creating a continuous facilitation of locomotion. Moreover, the duration of electrically induced locomotion in the cat had a limited duration, in the order of minutes for the cat (Shik et al. 1966; Garcia-Rill 1986, 1991), and seconds for the rat (Skinner and Garcia-Rill 1984). It is difficult to extrapolate from these animal studies to the potential effects of continuous DBS.

3.2.4 Location of stimulation—A great deal of confusion regarding the optimal site(s) for inducing locomotion following mesopontine stimulation has resulted. The initial report describing the MLR localized the optimal locomotion-inducing sites in the lateral cuneiform nucleus, but NOT in the medial cuneiform nucleus. This is important because recent studies have suggested that medial cuneiform sites were effective in inducing locomotion in the cat

(Takakusaki et al. 2004). However, our studies supported the initial findings by Shik and Orlovski, and confirmed that only lateral sites, and NOT medial sites, were effective in the cat (Garcia-Rill 1986, 1991) as well as the rat (Skinner and Garcia-Rill 1984). With the advent of histochemical labeling of PPTg cholinergic neurons using NADPH diaphorase, we undertook to verify if our stimulation sites were located near NADPH-D-positive PPTg neurons. Sagittal views of the PPTg, the optimal manner for visualizing the entire nucleus in as few sections as possible, revealed that these sites were in apposition or within NADPH-d-positive cell bodies (Garcia-Rill et al. 1985). We later confirmed this observation using choline acetyltransferase (ChAT) immunocytochemistry (Garcia-Rill et al. 1987). The key to understanding this result is that the posterior part of the PPTg actually intermixes and is located well dorsally within the lateral cuneiform (Garcia-Rill et al. 1987; Garcia-Rill and Skinner 1991). More recent studies reported that ChAT-positive cells were ventral to their locomotion-inducing sites, however, these authors performed labeling on 4 animals and failed to verify the location of these sites in all their animals (Takakusaki et al. 2004). Accurate labeling of PPTg cells shows that these are located well dorsal to the peduncle, and within locomotion-inducing sites (Garcia-Rill et al. 1987, Fig. 3, pg. 735).

A major difference between animal studies and DBS in humans is the approach of the electrode. Animal studies approach the midbrain dorsally into the inferior colliculus, through the cuneiform nucleus, and into the PPTg across its long axis. Human DBS involves an approach along the length of the brainstem through the posterior thalamus, the anterior midbrain, and along the long axis of the PPTg. Therefore, testing of sites dorsal (cuneiform) or ventral to the PPTg (midbrain reticular formation) is unlikely. That is, the surgeon must decide which site to aim for and will not bet the chance to test sites around the PPTg. The reader is referred to Fig.1 below that shows a three dimensional reconstruction of the Human PPTg in comparison to the approach used in animals.

4. Future Directions

A theoretical consideration that arises from our clinical experience is whether the PPTg may be considered a primary target, like the STN, rather than a simple stereotactic reference point represented by a neuronal population not well confined and embedded in a region crossed by several fiber systems. A no less important consideration concerns the PPTg itself, as the loss of PPTg neurons in PD appears to be in contrast with a therapeutic effect based on changes in electrical properties of neurons induced by stimulation, externally applied through the DBS lead. Thus, we have to consider more convincing possibilities on the potential mechanisms of action of PPTg DBS, which may involve the whole region in which PPTg neurons are embedded.

Likewise, it is difficult to grasp that there is a selective action of the electric field generated by a lead when that lead is larger than the PPTg itself. Moreover, the nucleus is close to structures that, when stimulated, are responsible for various motor and non-motor effects. Thus, the PPTg may be considered as a neurosurgical reference point in the brainstem, that, when stimulated, may induce clinical effects owing to its position and anatomical connections. In the light of the above considerations, the concern arises that it may be hazardous to ascribe to the PPTg the same role as the clinical, theoretical interpretations, and significance widely accepted for stimulation of the STN (Breit et al. 2004; Chaturvedi et al 2006; de Paor et al. 2009; Modolo et al. 2009; Okun et al. 2009; Volkmann et al. 2009; Moro et al. 2010).

In any case, the relevance of our PPTg experience arises also from a reinterpretation of the mechanism of action of DBS in PD and in other pathologies, as demonstrated also by the applications of DBS in psychiatric disorders. In conclusion, neurophysiological and clinical

observations obtained in implanted patients suggest new directions and open new horizons for the treatment of neurological and psychiatric disorders other than PD.

Finally, a critical consideration that must be addressed is the actual dimensions of electrodes for DBS. The size of the electrodes used in animal experiments is in the order of microelectrodes of a few microns to 100 μ m wires, an order of magnitude smaller than electrodes currently available for DBS (1.28 mm). The PPTg is far too small to be stimulated effectively, and without lesioning, using such electrodes. Manufacturers need to create smaller electrodes for DBS in such regions. The preceding discussion on the duration and frequency of stimulation suggests that, if the point is to excite the PPN, then long duration (200–500 msec) and low frequency (40–60 Hz) pulses should be used. On the other hand, if the point is to inactivate the PPN, then short duration (<200 msec) and high frequency (>60 Hz) pulses would be more effective. Overall, the parameters of stimulation currently used by most groups suggest that DBS of the PPN is inducing decreased PPN activity. Given that some findings in PD patients suggest that the PPN is overactive in PD (Teo et al. 1996, 1997), such stimulation may result in dampening PPN activity. An additional concern when considering stimulation using long duration (>200 msec) pulses is the potential damage that could be induced by such stimuli.

An anecdotal observation rarely mentioned is that, in the decerebrate animal, the bladder must be expressed before locomotion can be induced. There may be some inhibitory interactions that need to be considered when applying this technology to human patients. If DBS effects in humans are not elicited or thresholds are higher, it may be behoove consideration of this unusual observation from the animal literature.

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Figure 1. Reconstructions of the PPTg (PPN)

On the left is a three-dimensional reconstruction of the PPTg (PPN) of the human. The blue lines denote sagittal sections from lateral to medial of the pons and posterior midbrain. The sections are oriented to show the superior colliculus (SC) and the inferior colliculus (IC) dorsally, with the fourth ventricle (IV) to the left. Cholinergic cells of the PPTg are shown as red spheres, with more medial locus coeruleus cells in yellow and most medial laterodorsal segmental cells in purple. The arrow denotes the approach of the electrode placement in the human. On the right is a reconstruction of a rat brain showing PPTg cells as orange spheres, substantia nigra cells as green spheres, locus coeruleus cells as purple spheres, and laterodorsal segmental cells as yellow spheres. Note that the dorsoventral approach in the rat or cat is through the inferior colliculus and overlying cuneiform nucleus, in contrast to the human approach in which only anterior midbrain tissue is broached. For electrodes to be centered on the cuneiform nucleus, the approach would need to be parallel to that for the PPTg, and only one target can be tested with each approach.