Hypermetabolism in the ventrolateral thalamus in unilateral Parkinsonian resting tremor: a positron emission tomography study

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Received 8 February 2001; received in revised form 26 February 2001; accepted 13 March 2001

Abstract

Tremorogenesis in Parkinson’s disease (PD) is assumed to involve a cerebral network including the thalamus. An imaging study was performed on eight PD patients with strictly unilateral resting tremor using fluorodeoxyglucose positron emission tomography coregistered to 3-dimensional magnetic resonance imaging. Increased metabolic activity of high statistical significance ($P < 0.001$) was found in the anterior ventrolateral nuclear group of the thalamus located contralateral to the tremor side. The metabolic changes significantly covaried with tremor amplitudes. For the first time, it could be demonstrated that thalamic metabolic changes associated with tremor in PD are localized in the ventral lateral anterior nucleus (VLa). The results are discussed with respect to previous studies on tremor generation.

Keywords: Parkinson’s disease; Positron emission tomography; Thalamus; Tremor

Resting tremor is a key feature of Parkinson’s disease (PD). The underlying pathophysiological mechanisms are not precisely understood, although it is generally assumed that Parkinsonian resting tremor is generated by a network of oscillating neurons in the CNS [6]. A number of structures seem to be included in this network. There is evidence that the sensorimotor cortex is involved in tremor generation. Recordings directly from the cortical surface [1] as well as magneto- and electroencephalographic recordings [7,19] revealed cortical activity related to Parkinsonian resting tremor. The basal ganglia seem to be an essential component of the tremor generating network. Experiments with MPTP-treated monkeys and results of stereotactic operations in humans suggest that the subthalamic nucleus and the internal pallidum play an important role in tremor generation [3,4].

It has also been assumed that Parkinsonian resting tremor is of thalamic origin [14]. The thalamus is the essential link between the basal ganglia and the cerebral cortex. Lesioning or electrically stimulating thalamic subnuclei such as the ventralis intermedius (VIM) or the ventralis oralis posterior (VOP) lead to a dramatic relief of Parkinsonian resting tremor [16]. Moreover, microelectrode recordings in the ventral thalamic nuclear group during stereotactic operations reveal tremor-correlated neuronal activity [12].

So far, the contribution of ventral thalamic subnuclei to the generation of Parkinsonian resting tremor has mainly been demonstrated by invasive manoeuvres during stereotactic interventions. Non-invasive studies using positron emission tomography (PET) in PD patients revealed a distinctive covariance pattern of cerebral regional metabolism including the thalamus, the lentiform nucleus, and cortical motor areas [5]. Moreover, by comparing PD patients with and without tremor [2] evidence was provided for a tremor-specific metabolic network including the thalamus, the pons and premotor cortical areas. However, discrimination between different thalamic subnuclei was not reported.

Here, we present a study on PD patients with unilateral resting tremor using $^{18}$F-fluoro-2-deoxy-D-glucose (FDG)-PET coregistered to 3-dimensional magnetic resonance imaging (3-D MRI). Eight patients (four male, four female;
average age 62.8, range 53–73 years) with idiopathic Parkinson's disease (PD) participated in the study. Patients were chosen because they showed a moderate, strictly unilateral (three on the left, five on the right) resting tremor as the dominant feature of PD. PD was considered as idiopathic in all patients since clinical features including asymmetry were typical, all patients responded to L-Dopa, there were no symptoms of other hypokinetic-rigid syndromes, and MRI did not show structural abnormalities. The severity of PD ranged between Hoehn and Yahr stages I and III, the Unified PD Rating Scale subscore 'resting tremor' ranged between 3 and 4. There was no evidence for a neurological disease other than PD. All patients gave their informed consent to participate.

Before imaging acquisition, tremor was recorded using standard electrophysiological techniques including electromyography (EMG) and accelerometry [11]. FDG-PET data were acquired under previously described standardized conditions [9] on a Siemens CTI ECAT EXACT tomograph (10.8 cm axial field of view, 6.8 mm full width at half maximum (FWHM)). The 3-D MRI data sets were acquired on a 1.5 T clinical scanner (Siemens, Vision) and consisted of 150 T1-weighted sagittal slices (sequence: FLASH). For Statistical Parametric Mapping, the MRI and PET image data were coregistered (see Ref. [9]) and then normalized to the 3-D stereotaxic grid by Talairach and Tournoux [18] using SPM99 (Wellcome Department of Cognitive Neurology, London, UK).

After smoothing using a $8 \times 8 \times 8$ mm Gaussian kernel, interindividual variations of global regional cerebral metabolic rate for glucose (CMRGlc) in the FDG-PET data were accounted for by normalizing the individual global CMRGlc to an arbitrary mean of 50 $\mu$mol/100 ml/min using an analysis of covariance (ANCOVA). The normalized FDG-PET data were compared to an age-matched normal data base constituted from 12 healthy subjects by computing a pixel by pixel $t$-statistics for detection of hypometabolic areas. The $t$-statistics was transformed to a normal statistics yielding a $Z$-score for each pixel. Only those voxel clusters were kept that showed threshold $t$-values corresponding to $P < 0.001$ in a single test and exceeded a minimal cluster size of 12 voxels. The resulting $Z$-score voxel clusters were projected onto the realigned MRI data set using the SPM projection routine which additionally displays the Talairach co-ordinates thus allowing anatomic identification [10].

PET data analysis was performed as single subject and as group analysis; for group analysis, the brains of the patients with left-sided tremor were flipped right-to-left. To test the hypothesis that thalamic changes in metabolism were correlated to tremor amplitudes, we performed an additional covariate analysis using SPM. Tremor amplitudes were quantified as signal-to-noise ratios (SNR) in the electromyogram spectra [8]. The values thus obtained were correlated to PET results by multi-subject covariate analysis within the SPM software.

EMG and accelerometry, as measured shortly before the PET experiment, revealed typical Parkinsonian resting tremor (of frequencies between 4 and 6 Hz) on one side and no relevant tremor on the other side. During PET scanning, all eight patients showed marked unilateral tremor as well. Quantified tremor amplitudes (SNR) varied between 6 and 299 [8]. Statistical parametric mapping of PET data revealed no areas of significant hypometabolism at $P < 0.001$. In the single subject analysis, significant focal hypermetabolism within the area of the thalamus contralateral to the tremor symptoms was found in five of the eight patients ($P < 0.001$). In the group analysis with regard to the tremor amplitudes as a covariate, this result held indicating a positive correlation of thalamic hypermetabolism and tremor amplitudes ($P < 0.001$). The center of focal hypermetabolism (area of global maximum) was localized in the anterior portion of the ventrolateral nucleus of the thalamus (approximately corresponding to the ventral lateral anterior nucleus (VLa) according to the Jones nomenclature, see Ref. [13]). The mean Talairach co-ordinates of the center were $x = -12$, $y = -8$, $z = 6$. Further hypermetabolic areas were localized in the cerebellum bilaterally and in the sensorimotor cortex of the hemisphere which showed thalamic hypermetabolism. The cerebellar hypermetabolism was located within the medial part of the anterior lobe i.e. mainly in the vermis and in the intermediate zone. This region is known to project to the thalamus via the cerebellar nuclei. The cortical hypermetabolic areas corresponded to the sensorimotor cortex i.e. its hand area, with the maximum Z-value being localized in the postcentral gyrus. Fig. 1 demonstrates a projection of the significantly hypermetabolic areas on the slice sections including the thalamus (Fig. 1a) together with an overlay on the SPM glass brain template (Fig. 1b).

Of special interest is patient J.D., a 72-year-old male who suffered from right-sided tremor-dominant hemi-PD. In the PET experiment, a highly significant ($P < 0.0001$) focal hypermetabolism in the left ventrolateral nucleus thalami ($x = -10$, $y = -6$, $z = 6$) was found. Since the tremor was drug-resistant, ventral thalamotomy was performed, resulting in complete tremor relief. A follow-up PET and 3-D MRI investigation was performed 3 months after surgery, tremor analysis at this point of time revealed physiological tremor on the right hand. 3-D MRI showed that the stereotactic lesion was localized in the posterior part of the ventrolateral thalamus, corresponding approximately to the ventral lateral posterior nucleus (VLP) according to the Jones terminology or to the nucleus ventralis intermedius (VIM) according to Hassler [13]. The region of thalamic hypermetabolism as revealed by the presurgical PET was localized slightly lateral and anterior to the stereotactic lesion (see Fig. 1c). In the post-surgical PET investigation, no statistically significant areas of focal hypermetabolism in the previous localizations or elsewhere could be found.

Our results are partly in agreement with a FDG-PET study on PD patients with bilateral tremor by Antonini et
al. [2] who found a tremor-specific metabolic network comprising the thalamus, pons, and premotor cortex. In unilateral tremor, it was possible to show that the contralateral (but not the ipsilateral) thalamus was activated. Besides thalamic activity, regional hypermetabolism was found in the cerebellum bilaterally and in cortical sensorimotor areas contralateral to the tremor. Cerebellar activation is not specific for Parkinsonian tremor, but can also be detected in other tremor disorders such as essential or orthostatic tremor [15,20]. The involvement of sensorimotor cortical areas in this tremor-associated network has been demonstrated in a number of studies using various imaging modalities [1,2,7,19] and is confirmed by our results.

Our findings provided evidence for hypermetabolism in specific thalamic subnuclei. It is well known from anatomical studies that the ventrolateral thalamic nuclei are connected to the basal ganglia (VLa or Vop) and to the cerebellum (Vlp or VIM) i.e. to structures which are assumed to be involved in tremorogenesis [13,17]. Accordingly, stereotactic surgery with lesioning or high-frequency stimulation of the ventrolateral thalamus leads to a marked relief of Parkinsonian tremor [16], and neuronal activity recorded in this localization during surgery has been shown to be tremor-correlated [12]. Our study supports these findings using a non-invasive approach by demonstrating hypermetabolism in the anterior part of the ventrolateral nucleus, approximately corresponding to VLa according to Jones or Vop according to Hassler [13]. This focal hypermetabolism is obviously associated with tremor, since it is covariant with tremor amplitudes as revealed by SPM analysis. Basically, the covariance is compatible with both a ‘tremorogenic’ role of the thalamus and with somatosensory stimulation of thalamic cells by proprioceptive afferences. There are two arguments suggestive of a tremor generating...
role of neurons in the ventrolateral thalamus: First, Lenz [12] showed that the vast majority of cells (78%) with tremor-related activity in Vop and VIM does not respond to sensory stimuli [12]. Second, the input to the ventrolateral thalamus is not primarily somatosensory, but originates from either the basal ganglia (VLa or Vop) or the cerebellum (VLp or VIM) [13,17].

Further evidence for the correlation of thalamic regional hypermetabolism with contralateral tremor was provided by the results in patient J.D. who underwent successful stereotactic surgery. First, no thalamic hypermetabolism could be detected in the follow-up PET after successful surgical tremor relief. Second, the focal hypermetabolism and the stereotactic lesion were localized close to each other in the ventrolateral thalamus. Nevertheless, there was no complete overlap between the two localizations. While the regional hypermetabolism seems to be situated in VLa or Vop, the stereotactic lesion is rather located in VIM. On one hand, these differences in localization might be due to the limited spatial resolution of PET, given by the FWHM of 6.8 mm. On the other hand, our findings might imply that tremor-related focal hypermetabolism is mainly located in a thalamic subnucleus receiving input from the basal ganglia (VLa or Vop), whereas the stereotactic lesioning was performed in a thalamic area receiving cerebellar input (VIM). This discrepancy is difficult to interpret. However, Lenz et al. [12] found neurons with tremor-related activity also in Vop. Moreover, cerebellar hypermetabolism was bilateral in our study whereas the thalamic hypermetabolism was only unilateral. This does not seem to be compatible with the assumption that the thalamic hypermetabolism is located in the cerebellar target nucleus VIM. It is a so far unsolved issue how a lesion in a thalamic subnucleus which is part of the loop between cerebellum, thalamus and cortex (VIM) can suppress tremor activity in the basal ganglia loop. One has to assume that the different loops are not completely segregated, but interact to some extent.

In summary, this is the first study on unilateral Parkinsonian tremor using PET. It could be non-invasively shown that the tremor is covariant with regional hypermetabolism in the ventral lateral anterior nucleus (VLa) of the contralateral thalamus. Thus, these findings contribute to the understanding of the central oscillatory network generating Parkinsonian tremor.