Influence of spinal cord injury on cerebral sensorimotor systems: a PET study

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Abstract

Objectives—To assess the effect of a transverse spinal cord lesion on cerebral energy metabolism in view of sensorimotor reorganisation.

Methods—PET and ^{18}F -fluorodeoxyglucose were used to study resting cerebral glucose metabolism in 11 patients with complete paraplegia or tetraplegia after spinal cord injury and 12 healthy subjects. Regions of interest analysis was performed to determine global glucose metabolism (CMRGlu). Statistical parametric mapping was applied to compare both groups on a pixel by pixel basis (significance level $P = 0.001$).

Results—Global absolute CMRGlu was lower in spinal cord injury (33.6 (6.6) $\mu\text{mol}/100 \text{ ml}/\text{min}$ (mean (SD)) than in controls (45.6 (6.2), Mann-Whitney $P = 0.0026$). Statistical parametric mapping analysis disclosed relatively increased glucose metabolism particularly in the supplementary motor area, anterior cingulate, and putamen. Relatively reduced glucose metabolism in patients with spinal cord injury was found in the mid-brain, cerebellar hemispheres, and temporal cortex.

Conclusions—It is assumed that cerebral deafferentation due to reduction or loss of sensorimotor function results in the low level of absolute global CMRGlu found in patients with spinal cord injury. Relatively increased glucose metabolism in brain regions involved in attention and initiation of movement may be related to secondary disinhibition of these regions.

Keywords: spinal cord injury; cerebral sensorimotor systems; positron emission tomography

Spinal cord injury may damage descending or ascending corticospinal tracts.¹ Depending on the level and extent of damage, patients may present with incomplete or complete loss of sensorimotor function of two or all four limbs. Whereas some patients recover from neurological deficit with time, other patients have persisting paraplegia or tetraplegia.²

The relevance of loss of sensorimotor function for the reorganisation of cerebral sensorimotor systems is not well understood. Clinical and neurophysiological studies provide evidence for reorganisation of the primary motor and sensory cortex in patients with spinal cord injury^{3,4,5} or amputees.⁶ However, the relation between cerebral reorganisation within these regions and neuronal activity of functionally associated brain areas is not known. In the present study, we used PET and the tracer ^{18}F -fluorodeoxyglucose to study regional cerebral glucose metabolism, which is a measure of regional synaptic activity.^{7,8} With this method it has been shown that circumscribed brain lesions may suppress glucose metabolism or blood flow of functionally related remote brain areas.⁹ Accordingly, we assumed that the deafferentation state after spinal cord injury may be followed by an altered pattern of cerebral glucose metabolism in paraplegic and tetraplegic patients.

Patients and methods

11 right handed patients with spinal cord injury (nine men, two women, seven paraplegic, four tetraplegic patients (mean (SD) age 31 (11) years, range 19–53 years) were

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Table 1 Clinical data of patients with spinal cord injury

Patient No	Para/tetra	Age (y)	Sex	Interval (months)	Lesion (rad)	Motor complete	Sensory complete	Medication
1	Para	21	M	28	Th6	Th6	Th9	Bac, Clon
2	Para	22	F	9	L1/L2	L2	L4	Mid, Oxy
3	Para	30	F	10	Th11/Th12	Th12	L1	Mid, Oxy
4	Para	34	M	6	L4	L5	S3	Cbz
5	Para	53	M	182	C3/Th5	Th3	Th7	Bac, Oxy
6	Para	41	M	190	Th4	Th6	Th6	None
7	Para	44	M	65	Th4/Th5	Th5	Th5	None
8	Tetra	19	M	22	C6	Th3*	Th3*	Clon
9	Tetra	23	M	5	C5/C6	C6	C8	Clon
10	Tetra	24	M	56	C5/C6	C7	V7	None
11	Tetra	33	M	37	C6/C7	C7	Th9	Bac

Interval = time interval between spinal cord injury and PET study; lesion (rad) = (upper/lower) level of radiologically documented vertebral damage; motor/sens complete = highest spinal segment of complete loss of sensorimotor function; Bac = baclofen; Clon = clonazepam; Mid = midodrin; Oxy = oxybutinin; Cbz = carbamazepin. *In this patient, bilaterally impaired motor and sensory function was present between C7 and T2, complete loss of function was present below T3.

Figure 1 Statistical parametric map projections showing areas with significantly higher (A) and lower (B) relative cerebral glucose metabolism ($P < 0.001$) at rest in 11 patients with spinal cord injury v 12 healthy subjects. Differences are displayed on sagittal, coronal, and transverse projections. VPC = vertical line through posterior commissure; VAC = vertical line through anterior commissure.

studied at rest five to 190 months (median 28 months) after spinal cord injury using PET and the tracer ^{18}F -fluorodeoxyglucose (FDG) (table 1). All patients had an immediate neurological investigation and a full neurological examination on the day of the accident including a full radiographic investigation of the spine. The severity of neurological deficit was rated using the American Spinal Injury

Association impairment scale.¹ According to this scale, paraplegia or tetraplegia was complete in each patient (no motor or sensory function is preserved below the neurological level and extends through S4-S5). From the clinical status and CT of the brain which was performed on the day of the accident, there was no evidence for additional brain injury. Dysaesthetic pain was present in one patient (4) but was satisfactorily treated with carbamazepine. For comparison, 12 right handed healthy subjects were studied (age 34 (11), range 23 to 61 years). The study was approved by the ethics committee of the University Hospital Balgrist.

DATA ACQUISITION

FDG PET was performed with a 933/04-16 tomograph (CTI, Knoxville, four rings, seven planes, 8 mm full width at half maximum (FWHM). The FDG was prepared as previously described.¹⁰ The head of a subject was positioned parallel to the orbitomeatal line and was placed in an individually moulded thermoplastic head support to minimise movement during scanning. After two 10 minute transmission scans with a $^{68}\text{Ga}/^{68}\text{Ge}$ ring source, 140 to 298 MBq FDG were given intravenously over three minutes with a constant infusion pump. Twenty four arterial blood samples were manually drawn from an indwelling catheter for determination of plasma radioactivity and glucose concentration. A scan protocol comprising one dynamic (16 time frames, 48 minutes) and one static (five minutes) emission scan was used, covering the whole brain at two positions and yielding a total of 14 adjacent planes with a plane to plane distance of 8 mm. With an autoradiographic method,¹¹ the cerebral metabolic rate of glucose (CMRGlucose; $\mu\text{mol}/100\text{ml}/\text{min}$) was calculated for both data sets, which were combined to form a contiguous volume of 14 planes, 11.2 cm field of view. With statistical parametric mapping 95, these slices were then interpolated to 26 planes of the standard stereotactic atlas coordinate system of Talairach and Tournoux.¹²

STATISTICAL PARAMETRIC MAPPING

This method has been described in detail by Friston *et al.*¹³ Briefly, after transformation to the stereotactic coordinate system, images were smoothed in 3D with a Gaussian filter with FWHM corresponding to the spatial resolution of the scanner (8 mm). Interindividual variations of global CMRGlucose were accounted for by normalising individual global CMRGlucose to an arbitrary mean (in our study $40 \mu\text{mol}/100 \text{ ml}/\text{min}$) using an analysis of covariance (ANCOVA). Normalised images of patients with spinal cord injury and healthy subjects were compared by computing a pixel by pixel t statistic. The t statistic was transformed to a normal statistic yielding a Z score for each pixel. Pixels exceeding the significance level of $P = 0.001$ are displayed in axial, sagittal, and coronal projections of a statistical parametric mapping. To test for a possible relation between time from spinal cord injury and

Table 2 Differences of cerebral glucose metabolism in patients with spinal cord injury and healthy subjects displayed as a statistical parametric map with a significance level of $P = 0.001$

Area	Talairach coordinates of peak differences			Z score of peak difference
	x	y	z	
SCI > Controls:*				
SMA (L)	-20	-4	+52	4.36
SMA (R)	+20	-4	+52	2.96
Anterior cingulate (L)	-10	+10	+44	4.01
Anterior cingulate (R)	+20	+18	+40	3.23
Putamen (L)	-22	-6	+8	3.66
Putamen (R)	+20	-2	+12	3.39
Sensorimotor cortex (R)	+26	-12	+52	2.96
SCI < Controls:†				
Midbrain (R)	+6	-20	-16	3.84
Cerebellar hemisphere (L)	-50	-44	-28	2.69
Cerebellar hemisphere (R)	+52	-64	-20	3.77
Lateral temporal cortex (L)	-58	-20	-16	3.55

*Relatively higher.

†Relatively lower CMRGlu in patients with spinal cord injury compared with controls. Coordinates: x = width, y = anterior-posterior, z = height; Z = Z score of statistical parametric mapping (see methods); R/L = right/left side of brain.

CMRGlu, the normalised images of all patients with spinal cord injury were compared with the time interval between spinal cord injury and PET studies by ANCOVA (significance level $P = 0.001$). It must be noted that—regarding the time interval—patients clustered into two groups (nine patients were studied between five and 65 months, and two patients were studied 182 and 190 months after spinal cord injury; table 1).

As with statistical parametric mapping, absolute values of cerebral glucose consumption were adjusted to an arbitrary mean, we also determined the CMRGlu ($\mu\text{mol}/100\text{ml}/\text{min}$) using elliptical regions of interest which were placed on the whole brain at the level of the thalamus and basal ganglia of the PET images transformed to the stereotactic atlas.¹² Global metabolic rates of glucose for patients with spinal cord injury and healthy subjects were compared by Mann-Whitney U test.

Results

Absolute global CMRGlu was significantly lower in patients with spinal cord injury than in healthy subjects (33.6 (6.6) $\mu\text{mol}/100\text{ml}/\text{min}$ *v* 45.6 (6.2) $\mu\text{mol}/100\text{ml}/\text{min}$, $P = 0.0026$, Mann-Whitney). The difference between drug treated ($n = 8$, global CMRGlu 32.6 (8.3)) and untreated patients with spinal cord injury ($n = 3$, global CMRGlu 35.4 (5.3) $\mu\text{mol}/100\text{ml}/\text{min}$) was non-significant (Mann-Whitney $P = 0.8808$). This suggests that the global CMRGlu difference between patients with spinal cord injury and healthy subjects does not result from drug treatment.

Statistical parametric mapping disclosed pixels with relatively higher CMRGlu in the frontal lobe of patients with spinal cord injury, which bilaterally mainly comprised the supplementary motor area, and which caudally extended into the anterior cingulate (Brodmann area 24), and more laterally towards the motor cortex. These differences were more pronounced at the left side of the brain. Also, a few pixels with relatively higher CMRGlu were disclosed bilaterally in the putamen (fig 1A). Circumscribed areas with relatively lower CMRGlu were found in the midbrain, cere-

Figure 2 CMRGlu, adjusted to an arbitrary global mean (see methods), in the left anterior cingulate (A) and midbrain (B) of patients with spinal cord injury (open squares) in relation to the time interval between spinal cord injury and PET study. For these regions, means (SD) of adjusted CMRGlu of healthy subjects are displayed at the right side of the plots (filled circle).

bellar hemispheres, and temporal cortex of patients with spinal cord injury (fig 1B). Table 2 lists the coordinates of peak differences. No differences between paraplegic and tetraplegic patients were found.

For the time interval between spinal cord injury and PET study, statistical parametric mapping analysis yielded decreasing CMRGlu values with time for the left anterior cingulate (x/y/z coordinates $-18/+18/+40$, Z score = 3.79) and left dorsal insular cortex ($-34/-34/+16$, Z score = 3.68). Figure 2A shows this for the anterior cingulate. Increasing CMRGlu with time was found for the left ($-8/-34/-24$, Z score = 3.18) and right ($+8/-32/-28$, Z score = 2.95) midbrain, as well as for the cerebellar vermis ($+4/-60/-8$, Z score = 2.66). Figure 2B shows this for the left midbrain.

Discussion

Our study shows a low absolute CMRGlu in resting patients with spinal cord injury.

Because sensorimotor function comprising locomotion and sensory feed back from spinal cord to the brain in our patient group is expected to be greatly impaired or even absent, low CMRGlu may reflect a state of sensory deafferentiation and loss of pyramidal projections in these patients. Superimposed on the reduced global CMRGlu, our data disclose a distinct regional pattern of CMRGlu in patients with spinal cord injury which differs from that of healthy subjects. Patients with spinal cord injury at rest show relatively higher glucose metabolism in brain regions which are involved in movement preparation and execution, as well as in intentional aspects of motor tasks, particularly in the supplementary motor cortex, putamen, and anterior cingulate (Brodmann area 32). In these regions, an increase in cerebral blood flow has been shown using PET and $H_2^{15}O$ in healthy subjects during the performance of motor tasks.^{14,15} Also, mental simulation of motor tasks or ideation of walking activates premotor cortical areas and basal ganglia.¹⁶ Therefore, patients with spinal cord injury, although partially or completely unable to move, show relative CMRGlu increases at rest in brain areas which are activated (according to blood flow measurement with PET) in healthy subjects before and during movement.

Given the coupling of regional CMRGlu and synaptic activity,⁸ relatively increased CMRGlu in the above mentioned regions of our patients could be attributed to overactivity of neurons which originate within, or which project to these regions. Accordingly, our results may reflect a relative disinhibition secondary to reduction or loss of afferent impulses—for example, from the spinal cord, thalamus, or parietal lobe.¹⁸ Neurophysiological experiments provide ample evidence that disinhibition mediates synaptic reorganisation. After sciatic nerve lesions in animals, early enlargement of receptive fields of the somatosensory cortex is attributed to a release of inhibition,^{19,20} and follows a characteristic time course.²¹ Similar results were obtained in human patients with spinal cord injury and in amputees.^{5,6} Likewise, during motor cortex reorganisation, the size of excitable motor areas increases after upper limb amputation.²² In addition, shoulder movement in subjects with traumatic upper limb amputation and phantom perception results in abnormal increases in blood flow in the primary somatosensory and posterior parietal cortex, which has also been attributed to a release of neurons from normal inhibitory control.²³ Whereas these data were obtained through stimulation or movement and were recorded mainly from the primary motor or somatosensory cortex, the cortical differences between patients with spinal cord injury and healthy subjects in our study at rest were found in premotor areas. Whether these findings serve a clear functional role in patients with spinal cord injury remains open.

By contrast with the relatively increased glucose metabolism in brain regions which initiate movement, glucose metabolism in the

cerebellum and midbrain was decreased. The cerebellum and certain midbrain relay nuclei participate in movement coordination and control.¹⁷ Accordingly, persisting impairment or absence of voluntary movement after spinal cord injury could explain reduced neuronal activity in these structures. In addition, our data suggest that abnormal CMRGlu shows a temporal correlation after spinal cord injury (fig 2). With increasing time from spinal cord injury, relatively high CMRGlu in the left anterior cingulate decreased, whereas relatively low CMRGlu in the brainstem increased, both regions approaching normal levels of relative CMRGlu. Whether these distinct time changes, which can be attributed to different aspects of movement (initiation, control), are generally present also in other parts of the motor system may be considered in a larger series of patients or in prospective studies.

Recovery from experimental spinal cord injury depends on the integrity of cerebral sensorimotor systems. Rats with spinal cord lesions show regeneration and anatomical plasticity of corticospinal neurons one to two months after treatment with antibodies neutralising myelin associated neurite growth inhibitory proteins.²⁴ Contact placing of regenerating neurons in the spinal cord is, however, abolished after ablation of the sensorimotor cortex in these animals, which indicates that cortical neuronal activity is mandatory for recovery.²⁴ Therefore, knowledge of the time course of regional cerebral activity after spinal cord injury in humans could have implications for a possible intervention once treatment regimens have developed.

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