Dopamine D2 receptor binding and cerebral glucose metabolism recover after d-penicillamine-therapy in Wilson’s disease

Abstract Regional cerebral glucose metabolism (rCMRGlc) and dopamine D2 receptor binding were measured in a 31-year-old, severely affected, untreated patient with Wilson’s disease of 3 years’ duration using positron emission tomography and [18F]deoxyglucose and [18F]methylspiperone ([18F]MSP), respectively. There was a severe reduction of striatal and extrastriatal rCMRGlc as well as of striatal [18F]MSP accumulation rate. After 1 year of treatment with D-penicillamine, striatal and extrastriatal rCMRGlc and striatal [18F]MSP accumulation rate reached almost normal levels. It is hypothesized that recovery of motor functions due to copper trapping therapy was associated with an increase in basal ganglia activity and a re-expression or upregulation of dopamine D2 receptors.

Key words Wilson’s disease - Positron emission tomography - Dopamine D2 receptor - Regional cerebral glucose metabolism - Functional recovery

Introduction

In Wilson’s disease (WD) the severity of neurological signs seems to be related primarily to the extent of copper deposition in the striatum [1]. However, the copper concentration in the cerebral and cerebellar cortex is of similar magnitude to that in the basal ganglia [2, 3]. Cerebral involvement in WD has recently been shown to be detectable using positron emission tomography (PET) to measure the regional cerebral metabolic rate of glucose consumption (rCMRGlc) [4–6].

The prominent involuntary movements in WD such as tremor, dystonia and chorea raise the question whether there is a dysfunction of the nigrostriatal dopaminergic system, as has been shown in other neurological and psychiatric diseases affecting the basal ganglia such as progressive supranuclear palsy [7, 8], neuroacanthocytosis and striatonigral degeneration [9, 10]. Autopsy analyses of patients with WD have found reduced striatal dopamine and tyrosine hydroxylase levels, pointing to an impairment of the dopaminergic system [11, 12]. In contrast to the above-mentioned progressive and degenerative cerebral disorders, WD can be adequately treated solely with copper trapping chelating agents such as d-penicillamine or triethylene tetramine [13, 14]. Most patients respond to therapy and even severe neurological symptoms can be reversed [15]. Using the radioactive labelled compounds 3-N-[18F]methylspiperone ([18F]MSP) for labelling dopamine D2 receptors and 2-[18F]fluorodeoxyglucose (FDG) for assessing the cerebral metabolic activity, we examined the viability of dopamine D2 receptor-bearing neurons in the basal ganglia in a patient with WD and demonstrated a marked effect of copper trapping therapy.

Materials and methods

Quantitative assessment of neurological signs

The severity of cerebral dysfunction was rated by a score as described by Hefter et al. [16] based on semiquantitative examinations of neurological signs and symptoms (degrees of dystonia, bradykinesia, gait and speech disturbances, oculomotor impairment, cerebellar signs, pathological reflexes, and degree of tremor).
A 31-year-old white caucasian man was admitted to the neurology ward at the end of 1991 for investigation of progressive tremor, dystonic movements mainly of both upper limbs, dysarthria, hypersalivation as well as psychomotor retardation for 3 years. At the time of admission the patient showed Kayser-Fleischer corneal rings on slit lamp examination, saccadic eye movements, a severe dysarthria, and continuous drooling. A cogwheel rigidity of his upper extremities, more pronounced on the left, was accompanied by mild spasticity and proximal paresis in his lower extremities, and a Babinski's sign on the right side. Deep tendon reflexes were mildly elevated on both sides. Flexor dystonia of both upper extremities was noticed in addition to choreiform hyperkinesia of both hands and feet. The patient had a postural tremor of the hands, fingers and left foot, as well as a wing-beating tremor of his right arm. There was overshoot on finger-to-nose testing in addition to intention tremor and dysdiadochokinesia.

A tremendous reduction of his wing-beating tremor was noted accompanied with the highest image activity were averaged. A background ROI which radioactivity in excess of non-striatal background activity was estimated according to the autoradiographic model [20] using the system \([2.2.2./K]^+ISF^-, CO_3^{2-}\) for anion activation as described by Hamacher et al. [23]. Radiochemical purity was > 97%; the specific activity was approximately 215 TBq/mmol (5900 Ci/mmol) at the end of synthesis. Dynamic scanning began at the start of tracer injection with serial scans of increasing time frames, initially every 10 s, summing up to 19 frames until minute 65, and three late frames from minutes 90 to 150. Striatal regions of interest (ROI) were defined by a 50% isointensity level of the maximal image activity in late time frames in which radioactivity in excess of non-striatal background activity was evident in the vicinity of the striatum. Values of two slices with the highest image activity were averaged. A background ROI was placed in the cerebellum for determining unspecific binding.

Tissue uptake and plasma data were analysed by the graphical method as described by Patlak et al. [24]. In addition to the uptake constant, striatal/cerebellar \([^{18}\text{F}]\text{MSP}\) ratios at 150 min after tracer administration were calculated. Results were compared with those obtained in a group of four normal male volunteers [mean age 30.2 (SD 9.9) years; 8 males, 9 females] using the computerized brain atlas [20]. Dopamine D2 receptors \((^{18}\text{F})\text{MSP\ accumulation}\) were measured dynamically for 150 min after a bolus injection of approximately \(200 \text{ MBq} \times [^{18}\text{F}]\text{FDG\ synthesized\ according\ to\ the\ procedure\ described\ by\ Hamacher\ et\ al.\ [18]}\). Twenty-minute PET scans of 14 image slices were centred at 45 min after injection according to the steady state of the FDG kinetics [19]. The \(r\text{CMRGl}\) was estimated according to the autoradiographic model [20] using a lumped constant of 0.52 [21]. The patient was studied with eyes and ears open during resting wakefulness, while the room lights were dimmed and room noise was minimized. The patient was asked not to close his eyes, to prevent him from sleeping. The \(r\text{CMRGl}\) of anatomically oriented regions of interests (using corresponding horizontal MR slices) was compared to the \(r\text{CMRGl}\) in a control group of 17 healthy volunteers [mean age 30.2 (SD 5.1) years]. Since the percentage of unchanged \([^{18}\text{F}]\text{MSP}\) in plasma declines rapidly, the "instablette-corrected" arterial blood curve was used for calculation of kinetic parameters of the radioligand [25, 26].