Effects of vinpocetine on the redistribution of cerebral blood flow and glucose metabolism in chronic ischemic stroke patients: a PET study

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Abstract

The pharmacological effects of the neuroprotective drug vinpocetine, administered intravenously in a 14-day long treatment regime, on the cerebral blood flow and cerebral glucose metabolism in chronic ischemic stroke patients (n=13) were studied with positron emission tomography in a double-blind design. The regional and global cerebral metabolic rates of glucose (CMRglc) and cerebral blood flow (CBF) as well as vital physiological parameters, clinical performance scales, and transcranial Doppler parameters were measured before and after the treatment period in patient groups treated with daily intravenous infusion with or without vinpocetine. While the global CMRglc values did not change markedly as a result of the infusion treatment with (n=6) or without (n=7) vinpocetine, the global CBF increased and regional CMRglc and CBF values showed marked changes in several brain structures in both cases, with more accentuated changes when the infusion contained vinpocetine. In the latter case the highest rCBF changes were observed in those structures in which the highest regional uptake of labelled vinpocetine was measured in other PET studies (thalamus and caudate nucleus: increases amounting to 36% and 37%, respectively). The findings indicate that a 2-week long intravenous vinpocetine treatment can contribute effectively to the redistribution of rCBF in chronic ischemic stroke patients. The effects are most pronounced in those brain regions with the highest uptake of the drug.

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Keywords: Vinpocetine; Positron emission tomography; Cerebral blood flow; Cerebral glucose metabolism; Stroke

1. Introduction

During the past decades numerous investigations have shown that vinpocetine (ethyl apovincaminate, a synthetic compound related to the Vinca minor alkaloid vincamine) is a potent neuroprotective agent [1–4]. It has a well documented effect on cerebral glucose metabolism and blood flow [5–13]. It also has well described vascular and rheological effects, including decrease in cerebral vascular resistance as well as positive changes on erythrocyte deformability and platelet aggregability [14–18]. Vinpo-
Vinpocetine is a widely used neuroprotective drug in neurological practice, especially in cerebrovascular diseases, including chronic ischemic stroke [19,20]. However, in spite of a body of accumulated clinical evidence on the neuroprotective effects and therapeutic usefulness of vinpocetine, the drug’s main pharmacological and physiological actions are still not understood in detail.

In an earlier PET study with [11C]-labelled vinpocetine [21] (Gulyás et al., 1999) we have demonstrated that vinpocetine passes the blood–brain-barrier readily and is heterogeneously distributed in different brain regions, indicating specific binding to certain sites in the brain. The highest regional level was seen for the thalamus, followed by the basal ganglia and cortical regions. The brain distribution of [11C]-vinpocetine was similar in the human brain when the labelled drug was injected intravenously [22] or when administered orally [23]. The brain distribution was demonstrably dissimilar to that of the [11C]-ethanol produced by the esterolysis of the vinpocetine structure [24]. The in vivo human data were confirmed by autoradiography measurements on post mortem human brain tissue as well [25].

An earlier PET investigation in chronic stroke patients has indicated that vinpocetine, administered in a single dose as i.v. infusion, raises regional cerebral metabolic rates of glucose in healthy brain tissue. This effect has been shown mainly to be due to changes in kinetic constants representing glucose uptake and release, and not due to direct effects on glucose metabolism expressed by hexokinase activity [26,27]. It has not been shown, however, how a longer treatment regime, usual in clinical practice, affects cerebral circulation and metabolism, and whether the changes in cerebral glucose metabolism and cerebral blood flow run parallel and correlate with each other or not.

The main objective of the present investigation was to explore in a “typical” clinical target group of vinpocetine treatment, chronic stroke patients, whether a 2-week long treatment regime with intravenously administered vinpocetine results in changes in global and regional cerebral blood flow and glucose metabolic rates and, if so, whether the changes may lie behind the clinical effects of the drug.

2. Materials and methods

2.1. Subjects

Fifteen ischemic chronic stroke patients participated in the present study. The investigations were performed at the Department of Neurology, the Central Laboratory for Nuclear Medicine, and PET Centre of the Debrecen University Medical School, whereas the final part of image processing and analysis was done at the Department of Neuroscience and Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institute. The patients (11 men, 4 women, mean age: 59.7±13.2 (1 S.D.) years, weight: 68.8±7.2 kg, height: 165.5±3.4 cm, BMI: 25.2±5.3) had an ischemic stroke (12.4±17.3 months), prior to the present investigations. The average volume of the primary stroke lesion was 74.3±61.9 cm³. The patients and their closest relatives were fully informed about the objectives, details, and risks of the study and they gave a written consent, in agreement with the Helsinki Declaration [28]. The study was approved by the Ethical Committee of the Debrecen University Medical School.

2.2. Experimental design and patient handling

The experimental design was double-blind. The experimental code was broken after the phase of image analysis. The present patient group was selected from a large pool of chronic stroke patients treated in the Department of Neurology of the Debrecen University Medical School. In each patient the infarcted region was in the territory of the middle cerebral artery (MCA).

For the purpose of the present study, the physical and neurological status of the selected patients were assessed by the Orgogozo Scale [29], the Scandinavian Neurological Scale (SNS) [30], the Motor-scale [31], and the Barthel Index [32]. MRI scan (T1, T2, PD), carotid Doppler sonography (CDS, Ultramark 4 Plus), and transcranial Doppler (TCD, at 50 mm depth above the main trunk of the MCA) and routine laboratory tests were performed. The study included a 15-day hospitalisation period. Following this period no further follow-up was performed on the patients.

The exact experimental protocol is in Fig. 1. All subjects received an intravenous infusion of 500 ml physiological solution (Salsol) for 45 min each day for 14 days. One original subgroup of the subjects (8 patients; “placebo group”) did not have any vinpocetine in the infusion, whereas the other original sub-group (7 patients; “vinpocetine group”) had 1 mg/kg body-weight vinpocetine (Cavinton®, Gedeon Richter, Budapest) in the infusion.

For the final analysis two subjects were excluded (one from the placebo and one from the vinpocetine group) on the basis of (i) technical problems (PET covering a too limited field of view of the brain) and (ii) suspicion for acute cerebrovascular events between the two scanning sessions. The final groups, used for image analysis, consisted of 7 (placebo group) and 6 (vinpocetine group) subjects. Detailed patient-data are shown in Table 1.

2.3. Scanning procedures

The canto-meatal line was used during the MR scan to position the head in the same way in the different scanners, i.e. that the transaxial image slices were parallel with each other in each imaging modalities. Each patient had MRI scan with a Shimadzu SMT-100×1.0 T scanner (T1, T2, and PD weighted images). During the MRI and PET investigations, the patients were equipped with an
individually moulded plastic head fixation helmet, which kept the head in an identical position during scanning [33,34]. Intravenous cannula was placed in the subjects’ cubital veins for taking venous blood samples for measuring the time activity curves of the tracer in the blood and plasma. The venous sample was used for further analysis following the technique described by Phelps et al. [35] and Huang et al. [36]. The sampling was done during the butanol-PET every 10 s for 2 min, whereas during the FDG-PET it was done at every 10 s in the first minute, every 15 s during the second minute, every 30 s during the third minute, at every minute up to the 15th minute, and at every 10 min thereafter, up to 60 min. The PET investigation was conducted under conditions of sensory suppression in a darkened room as defined by Roland and Friberg [37]. In the first instance a butanol-PET measurement was made, followed by an FDG-PET scan. The time-delay between the two scans was, on the average, 45 min. The quantitative PET measurements were made on a GE 4096 Plus whole body positron camera with 5 mm in-plane resolution and 6.5 mm inter-slice distance [38]. The axial field-of-view of the camera is 103 mm. The camera produced 15 transaxial slices of the brain. $^{18}$F-deoxy-D-glucose (FDG) and $^{15}$O-butanol were used as metabolic and blood flow tracers, respectively. The tracers were produced by a standard procedure [35,39] and were administered in a bolus injection (administered radioactivity in one bolus injection: FDG: 10 mCi, butanol: 45 mCi). The data acquisition with the PET camera and blood sampling were initiated synchronously with the bolus injection. In the emission scans, data were collected for a total of 2 min in the butanol-PET and for 60 min in the FDG-PET. The PET images were reconstructed with a Hanning filter to an effective image resolution (FWHM) of 5 mm using attenuation correction obtained from a separate transmission scan. The time activity curves of the tracer in the blood were calculated on the basis of interval measure-

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vinpocetine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Pulse (min$^{-1}$)</td>
<td>82.29 ± 3.20</td>
<td>77.14 ± 2.86</td>
</tr>
<tr>
<td>Systolic pressure (Hg mm)</td>
<td>142.86 ± 5.67</td>
<td>130.00 ± 5.10</td>
</tr>
<tr>
<td>Diastolic pressure (Hg mm)</td>
<td>87.14 ± 2.67</td>
<td>80.00 ± 2.89</td>
</tr>
<tr>
<td>Htk (%)</td>
<td>0.39 ± 0.01</td>
<td>0.39 ± 0.02</td>
</tr>
<tr>
<td>Hgb</td>
<td>136.29 ± 5.80</td>
<td>124.42 ± 6.33</td>
</tr>
<tr>
<td>Barthel scale</td>
<td>85.71 ± 7.53</td>
<td>87.14 ± 6.76</td>
</tr>
<tr>
<td>Orgogozo scale</td>
<td>75.71 ± 8.19</td>
<td>78.57 ± 8.27</td>
</tr>
<tr>
<td>SNS scale</td>
<td>45.14 ± 3.28</td>
<td>46.14 ± 3.79</td>
</tr>
<tr>
<td>Motor scale</td>
<td>10.29 ± 1.25</td>
<td>10.86 ± 1.30</td>
</tr>
<tr>
<td>CDS, affected side (mm · sec$^{-1}$)</td>
<td>51.43 ± 17.25</td>
<td>33.33 ± 19.52</td>
</tr>
<tr>
<td>CDS, contralateral side (mm · sec$^{-1}$)</td>
<td>32.86 ± 16.68</td>
<td>33.33 ± 14.86</td>
</tr>
<tr>
<td>TCD, affected side (mm · sec$^{-1}$)</td>
<td>54.80 ± 10.63</td>
<td>62.0 ± 13.46</td>
</tr>
<tr>
<td>TCD, contralateral side (mm · sec$^{-1}$)</td>
<td>64.00 ± 4.07</td>
<td>71.33 ± 6.03</td>
</tr>
</tbody>
</table>

Differences are not significant at the $p<0.05$ level.
ments of tracer activity in blood samples taken manually from the patients.

2.4. Image data processing and analysis

On the basis of the PET measurements and the time activity curve of the tracer in blood, regional cerebral radioactivity concentrations were transformed in each patient into quantitative measurements of regional cerebral glucose metabolic rates and related kinetic constants in volumes-of-interest (VOI), using an updated version of the Kuwabara-model [40], with a fixed lumped constant (LC=0.42) in each patient [41]. The possible reposition errors between the two PET scans, due to the limitations of the head fixation helmet, were corrected by the automated algorithm of Woods et al. [42], as is described by Emri et al. [43]. The butanol scans were reconstructed with a dedicated software (McConnell Imaging Center, Montreal Neurological Institute), based upon the two-compartment model of Ohta et al. [44].

The MRI scans and the reconstructed CMRgic and CBF images were then processed with the help of the Karolinska Institute’s Human Brain Atlas (HBA) system [45]. In the first step, the individual MRI images were adjusted to the Talairach stereotactic coordinate system so that the main axes and planes of the brain were aligned with those of the Talairach system [46], but the individual images were not standardised in shape and size. Following the alignment of MRI images with the contours of the HBA standard brain, the PET images were also aligned stereotactically. The VOIs were drawn in the stereotactically aligned brains.

On the individual MRI scans (T2 images) a series of VOI’s were defined by two independent expert observers, covering the following regions: whole affected hemisphere, whole contralateral hemisphere; in the contralateral hemisphere: frontal, parietal, temporal, occipital cortex, thalamus, putamen, caudate nucleus, cerebellum, brainstem; in the affected hemisphere: stroke regions, a healthy region outside the stroke region in the supply territory of the anterior cerebral artery, thalamus, cerebellum, brainstem were analysed. The VOIs, determined in the individual MRI scans, were transferred to the individual PET images and parametric data (rCBF, rCMRgic) were calculated inside the VOIs. Averages and standard errors of mean

![Fig. 2. MRI and PET images of a patient from the placebo group. Horizontal slices, 7 mm above the AC–PC axis. Radiological convention (left hemisphere in the right side; R—right, L—left). (A) T1 weighted MR image. (B) T2 weighted MR image. CBF images before (C) and after (D) treatment. CMRgic images before (E) and after (F) treatment. Stroke region in the left hemisphere.

Fig. 3. MRI and PET images of a patient from the vinpocetine group. Horizontal slices, 7 mm above the AC–PC axis. (A) T1 weighted MR image. (B) T2 weighted MR image. CBF images before (C) and after (D) treatment. CMRgic images before (E) and after (F) treatment. Stroke region in the right hemisphere.]
3. Results

3.1. Basal values and changes in cerebral blood flow

The T1 and T2 weighted MR images (examples in Figs. 2A and B; 3A and B) clearly show the lesioned region in the brain, whereas the metabolic and flow PET images display the reduced rCBF in the stroke region before treatment (Figs. 2C and E; 3C and E), and the relative increases in flow after treatment (Figs. 2D and 3D), as well as the baseline situation and changes in glucose metabolism (Figs. 2F and 3F).

Table 2

<table>
<thead>
<tr>
<th>Region</th>
<th>CBF (ml/100g/min) Before</th>
<th>CBF (ml/100g/min) After</th>
<th>Δ%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain</td>
<td>45.41 ± 6.01</td>
<td>48.49 ± 6.88</td>
<td>3.46%</td>
<td>0.74</td>
</tr>
<tr>
<td>Thalamus</td>
<td>78.30 ± 10.52</td>
<td>80.77 ± 9.58</td>
<td>3.16%</td>
<td>0.83</td>
</tr>
<tr>
<td>Putamen</td>
<td>70.96 ± 10.39</td>
<td>72.83 ± 10.05</td>
<td>2.64%</td>
<td>0.90</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>68.89 ± 12.53</td>
<td>66.07 ± 9.24</td>
<td>-2.90%</td>
<td>0.87</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>63.99 ± 12.76</td>
<td>65.59 ± 8.19</td>
<td>2.50%</td>
<td>0.92</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>66.37 ± 14.73</td>
<td>65.93 ± 11.22</td>
<td>-0.67%</td>
<td>0.99</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>69.16 ± 14.82</td>
<td>66.16 ± 9.93</td>
<td>-3.43%</td>
<td>0.88</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>66.59 ± 11.38</td>
<td>66.83 ± 9.48</td>
<td>0.36%</td>
<td>0.99</td>
</tr>
<tr>
<td>Mesencephalon</td>
<td>49.93 ± 5.23</td>
<td>50.60 ± 7.63</td>
<td>1.37%</td>
<td>0.50</td>
</tr>
<tr>
<td>Pons</td>
<td>46.26 ± 4.22</td>
<td>50.37 ± 5.54</td>
<td>8.89%</td>
<td>0.39</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>51.21 ± 4.20</td>
<td>56.10 ± 5.41</td>
<td>9.54%</td>
<td>0.52</td>
</tr>
</tbody>
</table>

The gCBF values in the whole patient group before treatment was 45.33 ± 3.63 ml/100 g/min. There was no significant difference in the basal gCBF values between the placebo group and vinpocetine group (45.41 ± 6.01 ml/100 g/min versus 45.23 ± 4.23 ml/100 g/min). The gCBF values after the 14 days treatment were 48.49 ± 6.88 ml/100 g/min in the placebo group and 55.83 ± 6.63 ml/100 g/min in the vinpocetine group; the differences not being significant (p values: 0.74 and 0.21, respectively).

The highest blood flow increases after treatment in the placebo group were found in the mesencephalon (13.76 ± 4.92%), pons (8.89 ± 4.16%), and cerebellum (9.54 ± 4.12%), whereas in the vinpocetine group they were found in the aforementioned structures (mesencephalon: 33.08 ± 6.54%; pons: 18.59 ± 8.31%; cerebellum: 28.26 ± 7.75%), and the unaffected thalamus (36.39 ± 17.55%), caudate nucleus (37.29 ± 15.38%), and the stroke region (33.89 ± 2.69%) (Table 2; Figs. 2 and 3). The 3-way ANOVA showed an apparent tendency for the increases in rCBF values after treatment, with special regard to the thalamus (F(5.55)=1.81; p<0.12). Nevertheless, the treatment-related changes in the contralateral hemisphere in the vinpocetine group showed a marked tendency for more accentuated increases (p values between 0.12 and 0.46) than in the placebo group (p values between 0.50 and 0.99) (Table 2). The comparison of the flow-differences (placebo group/pre- vs. post-treatment/ as compared to the respective values in the vinpocetine group) also indicated a strong tendency, namely that the flow increases in the vinpocetine group tend

(S.E.M.) were calculated. The statistical analysis was a two-tiered VOI-based ‘hypothesis driven’ or ‘biassed’ statistics. First, the metabolic (rCMRglu) and flow (rCBF) data were analysed with ANOVA, using a three-way interaction (1: before and after treatment, 2: placebo and vinpocetine, 3: VOIs: cortical hemispheres, cerebellar hemispheres, thalamus, basal ganglia). After obtaining only trends towards significance (p<0.05) using ANOVA (see Results and Discussion), in order to limit the target-volume of the statistical procedure, we assessed the statistical differences between (i) the placebo group and the vinpocetine group VOI-values and (ii) the pre- and post-treatment values within the respective groups with a Student t-test (two-tailed; paired or homoscedastic, depending upon the respective data sets).
to markedly exceed those in the placebo group (for the basal ganglia, thalamus, mesencephalon, occipital and frontal cortex, and whole unaffected hemisphere: p<0.25).

### 3.2. Basal values and changes in cerebral glucose metabolism

The basal whole-brain CMRglc values (shown in Table 3) were 6.96±0.37 in the whole patient group, 7.30±0.32 mg/100 g/min in the placebo group and 6.50±0.73 mg/100 g/min in the vinpocetine group (p=0.32). Following the infusion, in contrast to the CBF changes, the CMRglc decreased globally as well as regionally in both patient groups (Table 3). In the affected hemisphere the CMRglc decreases were more expressed in the placebo group than in the vinpocetine one. This effect was seen principally in the stroke region (3-way ANOVA analysis: (F(5.5)=0.39; p<0.85); the pair-wise t-tests are shown in Table 3).

### 4. Discussion

The main purpose of the present study was to measure with PET the effects of vinpocetine administered daily i.v. in course of a 2-week long infusion regime on the magnitude of cerebral blood flow and metabolism. By using multiple tracers for labelling different physiological–biochemical functions in the human body, PET can provide us with a unique insight into the correlation between metabolism and blood flow. In the present case we have used [18F]-FDG for measuring glucose metabolism and [15O]-butanol for measuring blood flow changes in the human brain. As complementary measures, additional physiological and clinical parameters have also been monitored and documented. The major clinical scales (Barthel, Orgogozo, SNS, Motor Scale) did not show any significant changes after the continuous vinpocetine treatment. Despite an increase in flow velocity in the MCA, the TCD related physiological parameters showed no significant change either following a 15 day long treatment. These are not surprising as the study population had an average time period between the acute stroke and the present study more than 1 year and can therefore be regarded as an established “chronic” patient population.

### 4.1. Changes in cerebral blood flow

The global CBF values (45.33±3.63 ml/100 g/min) in the whole patient group were above as those published for the aged-matched normal population (37.3 ml/100 g/min, Ref. [52]). This is an unexpected finding, because our patients had relatively large lesions (11.9±9.2% of the affected hemisphere), and lower gCBF values would have been expected which were not found in our PET measurements. It should be noted here that the haematocrit values of the patients (39.0±1.0) were significantly lower (p≤0.05,
Wilcoxon-test) than the physiological value in the normal population (42.3±2.7, Ref. [47]). As decreases in haematocrit values result in increased CBF values [48], this fact in the present case may explain the higher than expected gCBF values in the patient population.

As expected, the rCBF values between the two hemispheres were significantly different. CBF in the affected hemisphere was lower than the gCBF values in age-matched controls. This is due to the large disfunctioning region in the affected hemisphere. On the other hand, the CBF in the contralateral hemisphere was markedly higher than the normal values in age matched control groups, and this relatively high CBF contributed to the aforementioned “pseudo normal” gCBF value of the whole patient group.

Generally speaking after the 2-week long treatment the gCBF values increased in both the placebo and the vinpocetine groups. There were marked but no significant differences between the two groups with respect to gCBF increases. This fact indicates that the gCBF increases may partly be due to the effects of the infusion which improves cerebral microcirculation and results in increased CBF in most structures following both control and vinpocetine infusion. Indeed, we have found in an earlier PET study that a single vinpocetine infusion has significantly increased the K1 and k2 glucose metabolic constants in the affected hemisphere. This was especially pronounced in the stroke region (33.89%), in the thalamus (21.75%), the mesencephalon (24.32%), and the cerebellum (25.94%), suggesting that vinpocetine promotes the redistribution of blood among brain structures.

4.2. Glucose metabolism before and after treatment

The pre-treatment global CMRglc values (6.96±0.37 mg/100 g/min) were reduced in stroke patients as compared to the aged matched healthy subjects (7.04–7.54 mg/100 g/min; Refs. [52,53]). The decreased global values are due to the marked CMRglc decreases in the affected hemisphere (6.08±0.39 mg/100 g/min), whereas the values in the contralateral hemisphere were in the range of age matched healthy subjects (7.56±0.40 mg/100 g/min).

Both the saline infusion and the vinpocetine infusion caused a slight non-significant decrease in gCMRglc values. It may reflect the well documented observation that an improvement in blood circulation results in an improved ratio between aerobic/anaerobic ATP synthesis [54]. The improved microcirculation results in more oxygen supply and in energy terms, its rate of work exceeds that of the glucose consumption decrease, according to the relevant Eq. (1) of Gjedde et al.:

\[ J_{\text{ATP}} = 2J_{\text{glc}} + 6J_{\text{O2}}, \]

where \( J_{\text{ATP}} \) is the ATP production, \( J_{\text{glc}} \) is the glucose consumption, and \( J_{\text{O2}} \) is the oxygen consumption [55].

This tendency was present in all structures in both hemispheres. The relative differences between the decreases in rCMRglc values were equivocal in the contralateral hemisphere. The pattern was uniform in the affected hemisphere, where in all structures the decreases in rCMRglc after vinpocetine infusion were less than those after placebo infusion. This indicates that vinpocetine improves glucose utilisation in the affected hemisphere. Indeed, we have found in an earlier PET study that a single vinpocetine infusion has significantly increased the K1 and k2 glucose metabolic constants in the affected hemisphere [26,27]. This observation has been supported by animal studies [56–58] as well as observations on humans [20].

Interestingly the metabolic post-treatment reduction was most intensive in the stroke region in the placebo (18%) group as well as in the Vinpocetine group (14%). This latter fact may point to the composite nature of the stroke region (including the “penumbra”): it may comprise metabolically a-functional (i.e. necrotic), hypo-functional, but also normo- and hyper-functional (i.e. regenerating) tissue compartments and the post-treatment metabolic changes may reflect the tissue reactivity in this functionally composite region [59,60].

Similarly to our observations of the effects of pure infusion on CMRglc, earlier PET investigations have also reported that drug-free infusion decreases glucose metabolism in the brain [61]. It is also noteworthy that during test-
retest reliability investigations with longer periods (6–35 weeks) between the two scans the second PET measurements showed decreased CMRglc values, though the differences were not significant [62,63].

5. Conclusion

Pure infusion increased gCBF and decreased, to some extent, gCMRglc. The global effects of the saline infusion on CBF indicate that, in line with earlier observations, isovolaemic infusion improves cerebral circulation and increases CBF. As a consequence of its beneficial circulatory effects, it also improves the ratio between oxidative phosphorylation and glycolytic ATP production [54], which may indeed result in a reduced gCMRglc measured with the FDG-PET technique. This fact, however, indicates an improved glucose metabolism, resulting in an increased aerobic/anaerobic glucose metabolic ratio.

In earlier studies [26,27] we have determined the kinetic constants K1 (the unidirectional blood–brain clearance of glucose, describing glucose uptake), k2 (the rate constant for the elimination of glucose from the brain), and k3 (the rate constant expressing hexokinase activity), in various brain regions of chronic ischemic stroke patients before and after vinpocetine treatment. Whereas there were no significant changes in k3, both K1 and k2 changed significantly in all brain regions with the exception of the stroke and the peri-stroke regions. These observations suggest the modulation of the glucose transporter in brain capillaries, which may stand behind the changes in rCMRglc observed in the present investigation, as well.

The vinpocetine infusion has also increased gCBF, but the changes were identical to that obtained with placebo infusion, indicating that this effect can predominantly be attributed to the infusion itself. However, the regional changes in cerebral blood flow after vinpocetine infusion, as compared to that obtained after placebo infusion, indicate that vinpocetine treatment results in a regional redistribution of cerebral blood flow, the blood flow increases are the highest in the thalamus, the basal ganglia, and the brain stem. The regional uptake of 11C-vinpocetine was the highest in these structures, indicating a correlation between the drug’s pharmacological and physiological effects, as well [22].

Vinpocetine has also decreased the gCMRglc, similarly to the effect of placebo infusion. However, the reduction of CMRglc was less after vinpocetine infusion than after placebo infusion. As indicated above, this can be explained by an improved aerobic/anaerobic glucose metabolic ratio. The decreased glucose consumption goes parallel with an improved glucose utilisation due to a positive shift in the aerobic–anaerobic glucose metabolic ratio. That is, due to an increased aerobic glucose metabolism less glucose molecule can produce identical amount of ATP than with a lower aerobic/anaerobic ratio. The regional changes in glucose metabolism were the highest in the affected hemisphere, similarly to the situation after a single infusion [26,27].

The present data confirm former observations on the decoupling between glucose metabolism and cerebral blood flow under pathological conditions [53]. Whereas placebo isotonic infusion improves cerebral blood circulation and by that way increases cerebral blood flow, as well as helps restore the physiological ration between oxidative/glycolytic ATP production, vinpocetine modifies this general and systemic effect by, most probably, its direct CNS effects. Vinpocetine, according to the present study, contributes to a regional redistribution of cerebral blood flow in such a manner that relatively more blood reaches those brain structures which, according to other studies, show high uptake of radiolabelled vinpocetine. Also, vinpocetine can regionally modify the utilisation of glucose in the brain and this effect is more pronounced in the affected hemisphere. These complex effects of vinpocetine indicate that the drug, by way of its direct CNS effects, can usefully contribute to the restoration of physiological conditions in stroke patients.

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