Cerebral blood flow thresholds for supply dependent glucose utilisation in traumatic brain injury: A multi-tracer 15Oxygen and [18F]-fluorodeoxyglucose positron emission tomography study

Jeroen Hermanniès,1 Young T Hong,2 Monica Trivedi,1 Joanne Outtrim,1 Franklin I Aigbirihio,2 Peter J Nestor,3 Tim D Fryer,2 David K Menon,1 Jonathan P Cole1

1University Division of Anaesthesia, University of Cambridge, Cambridge, UK. 2Wolfson Brain Imaging Centre, Department of Clinical Neurosciences, University of Cambridge, Addenbrooke’s Hospital, Cambridge, Cambridge, UK. 3German Center for Neurodegenerative Diseases, Magdeburg, Germany.

Introduction

Metabolic derangements are common after traumatic brain injury (TBI) and not always the consequence of classical ischaemia. Few studies have combined [18F]-fluorodeoxyglucose (FDG) and multi-tracer oxygen-15 ([15O]) positron emission tomography (PET) to interrogate underlying pathophysiological mechanisms.1,2 We examined how derangements in FDG kinetic parameters within injured brain relate to cerebral blood flow (CBF), oxygen metabolism (CMRO2), oxygen extraction fraction (OEF) and plasma glucose.

Methods

Twenty-six TBI patients underwent combined [15O] and FDG PET on 34 occasions; 10 and 9 healthy volunteers underwent [15O] and FDG PET respectively (Table 1). All scans were performed on a General Electric Advance scanner (GE Medical Systems, Milwaukee, WI, USA) and processed.3 Standard models were applied to [15O] data to produce CBF, CBV, CMRO2, and OEF maps. The following rate constants were determined with an irreversible two-compartment model (Figure 1): transport across the blood brain barrier (K1, k2), hexokinase activity (k3), and influx rate (K). Patient data were coregistered with CT and regions of interest (ROIs) defined (Figure 2) for haemorrhagic lesion (core), hypodense tissue (penumbra), 1 cm border zone of normal appearing tissue (peri-penumbra), and all other normal appearing tissue (normal) for comparison with a mixed grey/white cortical ROI in healthy volunteers (control). Regional k3 increases (hot-spot ROIs) were defined as those voxels above the upper 95% confidence interval threshold calculated for each subject using the mean plus 2 standard deviations (SD) of all voxels within normal appearing brain and compared with the ischaemic brain volume (IBV) within patients.4

Results

-K1 was reduced within core, but comparable to control values in peri-penumbra and normal ROIs (Table 2). -While k3 and K were lower than control values, regional increases were found in the vicinity of lesions and structurally normal areas (Figure 2). -There was a clear relationship between glucose transport, as measured by K1, and CBF (R² 0.65, p<0.001 linear regression Figure 3A). K1 variability was best explained by CBF within core and penumbra (R² was 0.82 and 0.48 respectively, both p<0.001) compared to peri-penumbra and normal (both R² 0.10, p=0.08 and 0.07). -There was a linear relationship between k3 and CBF (R² 0.12, p<0.001) but this was not significant within individual lesion based ROIs -K1 was significantly below 95% confidence intervals for control values when CBF < 25ml/100ml/min (Figure 3) -k3 hot-spots showed higher K1 and lower CBF than normal patient brain (0.101 vs. 0.091 ml/min, p=0.03 & 25.0 vs. 28.4 ml/100ml/min, p<0.001) - Hot-spots showed little evidence of ischaemia (Dice similarity coefficient for ischaemic brain and hot-spot volume was 0.01 (IC 0.02) - Low plasma glucose was associated with increased k3 and K1, R² 0.11 and 0.27, p<0.001.

Summary

-In patients, glucose delivery (K1) was dependent on supply with significantly lower values occurring below a threshold CBF of 25ml/100ml/min. K1 was particularly driven by CBF within lesion core and penumbra where CBF values were lower -Changes in hexokinase activity (k3) were variable across the injured brain and not driven by CBF. While k3 hot-spots were found close to lesion, they were often found within normal appearing brain. While such regions tended to have lower CBF it was rare to find increases in OEF consistent with cerebral ischaemia -Low plasma glucose in patients tended to be associated with increases in k3 and K1, and may be a sign of metabolic stress

Conclusions

These findings demonstrate that while glucose utilisation is reduced within the vicinity of lesions due to low CBF and impaired glucose delivery, regional increases in utilisation occur across the injured brain and result from a rise in hexokinase activity (k3). Such increases occur in the absence of classical ischaemia and are associated with lower blood glucose values.

Table 2: Values are median (IQR) ± Kruskal-Wallis test for comparison between core, penumbra, peri-penumbra and normal ROIs within patients. † Mann-Whitney U test for comparison between the normal ROI in patients and control.

Summary

In patients, glucose delivery (K1) was dependent on supply with significantly lower values occurring below a threshold CBF of 25ml/100ml/min. K1 was particularly driven by CBF within lesion core and penumbra where CBF values were lower.

Changes in hexokinase activity (k3) were variable across the injured brain and not driven by CBF. While k3 hot-spots were found close to lesion, they were often found within normal appearing brain. While such regions tended to have lower CBF it was rare to find increases in OEF consistent with cerebral ischaemia.

Low plasma glucose in patients tended to be associated with increases in k3 and K1, and may be a sign of metabolic stress.

Conclusions

These findings demonstrate that while glucose utilisation is reduced within the vicinity of lesions due to low CBF and impaired glucose delivery, regional increases in utilisation occur across the injured brain and result from a rise in hexokinase activity (k3). Such increases occur in the absence of classical ischaemia and are associated with lower blood glucose values.

References


Figure 1: irreversible 2-compartment model. K1 is calculated as K1=K3/(k2+k3)

Figure 2: CT scan, [15O] and FDG kinetic parameters obtained in a 29-year old male with severe TBI within 24 hours following a road traffic accident. Plasma glucose is 6.6 mmol/l. A) The CT demonstrates haemorrhagic contusions. Regions of interest (ROIs) are defined for haemorrhagic lesion (core, red), hypodense tissue (penumbra, blue), 1 cm border zone of normal appearing tissue (peri-penumbra, green). B) Physiological maps of CBF, CMRO2, OEF, K1, K2 and k3. Areas of increased hexokinase activity (k3 hot spots’) and ischaemic brain volume are superimposed on the CT scan.

Figure 3: (A) ROI based relationship between K1 and CBF plotted for all ROIs separately (Blue = core, green is penumbra, brown is peri-penumbra and purple is normal appearing. Horizontal dotted lines and shaded box indicate upper and lower 95% confidence interval (CI) for healthy control K1 values with the vertical line showing CBF <5 ml/100ml/min. B) Individual voxel based locally weighted scatterplot smoothing based on all image voxel data for relationship between CBF and K1. Each line represents one scan.