Hyperglycemia and ischaemic stroke

Elevated blood glucose in the hyper-acute phase after onset:

- Occurs in over a third of stroke patients
- Associated with large infarct size, poor functional outcome and higher risk of mortality

Question:
- What are the mechanisms of harm?
Rodent Models of Focal Cerebral Ischaemia

Permanent middle cerebral artery occlusion

Transient middle cerebral artery occlusion

Examine influences on penumbra

Examine influences on reperfused tissue
Hyperglycemia exacerbates ischaemic brain damage in rats

Early lesion growth by DWI MRI

Infarct volume by T2 MRI (24h)

Vehicle

Glucose

Roy et al, unpublished

Is the increase tissue damage due to more severe reductions in CBF?
Hyperglycemia does not influence the severity of ischaemia

Perfusion-weighted MR imaging of CBF over time

1 hour

4 hours

Tissue < 30 ml/100g/min

Roy et al, unpublished

In vivo autoradiography of CBF – 1h after arterial occlusion

Threshold analysis

ROI analysis
Does circadian desynchrony adversely affect stroke outcome?

- Circadian desynchrony occurs after jet-lag and shift work
- Associated with physiological changes that impact on stroke e.g. hyperglycemia, hypertension, metabolic syndrome

Causes of post-stroke hyperglycaemia:

- Stress response to the hypoxic insult
- Undiagnosed disorder of glucose metabolism
No effect of photoperiod disruption on vulnerability to focal cerebral ischaemia in rats

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Background & Aims

- Circadian rhythms are daily oscillations in physiology and behaviour that recur with a period of 24 h.
- Master clock in suprachiasmatic nucleus (SCN) synchronises internal rhythm to environmental stimuli.
- Manipulation of the light/dark cycle such as in photoperiod disruption (PD) results in circadian misalignment.
- Shift work involves PD such that exposure to light/dark cycles are regularly altered compared to normal day/night schedules.
- PD induces changes in metabolism or physiology (e.g. hypertension, hyperglycaemia)¹ ² that have the potential to adversely affect stroke outcome.

Methodology

- Animals: adult male Wistar rats (200-250g); housed singly under two different light/dark conditions (n=12 each).
- Six hour phase advance protocol: for PD rats; lights switched on 6 h earlier than previous photoperiod every 3 days for 9 weeks.
- Locomotor activity: monitored continuously by infrared movement sensors to examine temporal associations between light/dark periods and activity only in PD rats.
- Physiological measurements: body weight and food intake measured weekly; systolic blood pressure (BP) recorded by tail cuff plethysmography at baseline and again 9 weeks later; blood glucose measured immediately following induction of isoflurane anaesthesia prior to permanent distal MCAO by diathermy. Plasma fructosamine measured at 48 h after MCAO.
- Model of cerebral ischemia: permanent distal MCA occluded using electrocoagulation, adapted from Tamura et al., 1981¹.
- MRI: infarct volume was assessed by T₂ weighted MRI 48 h following MCAO by an experimenter.

Results

- Control and PD rats displayed comparable body weight gain and food intake.
- No effect of PD on infarct size after permanent MCAO.
- PD did not affect plasma fructosamine levels.
- PD had no effect on blood glucose immediately prior to MCAO.

Conclusions

- PD resulted in temporal dissociation between light/dark cycle and activity but had no effect on key physiological parameters that can impact on infarct size.
- There was no effect of PD on infarct size after MCAO in young healthy rats.
- Potentially adverse effects of PD such as occurs in shift work, on stroke outcome may require the presence of existing co-morbidities.

References


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Rodent Models of Focal Cerebral Ischaemia

Permanent ischaemia

Ischaemia with reperfusion

No effect of photoperiod disruption

+ hypertension
Immune response is major contributor to ischaemia + reperfusion pathobiology

The role of microglia and myeloid immune cells in acute cerebral ischemia. Front Cell Neurosci. 2015;8:461

Microglial activation induced by circadian desynchrony

Wyse, Biello et al, unpublished
Does circadian desynchrony “prime” the immune system to exacerbate damage after ischaemia + reperfusion?

Vascular?

Systemic Inflammation Impairs Tissue Reperfusion Through Endothelin-Dependent Mechanisms in Cerebral Ischemia

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What do we need?

Immunology expertise and techniques for tissue/blood analysis