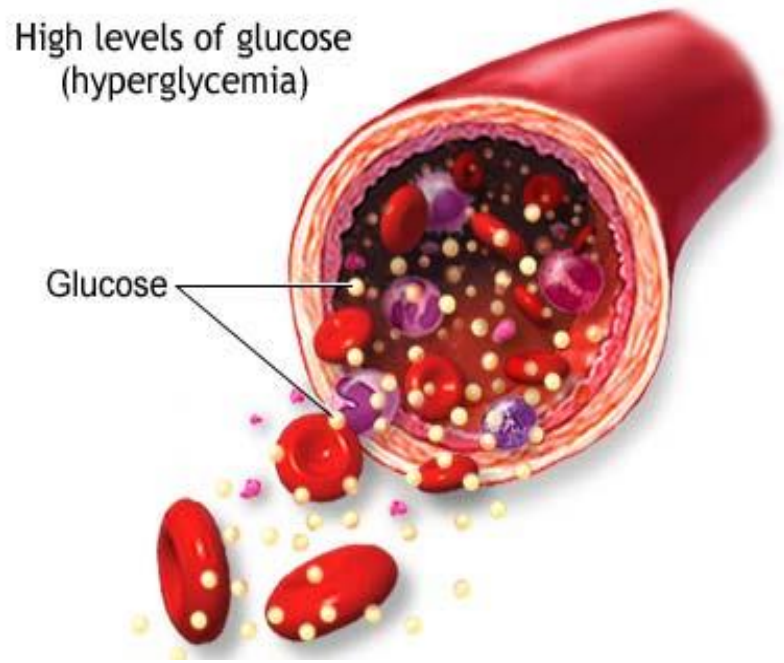
Hyperglycemia and ischaemic stroke

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

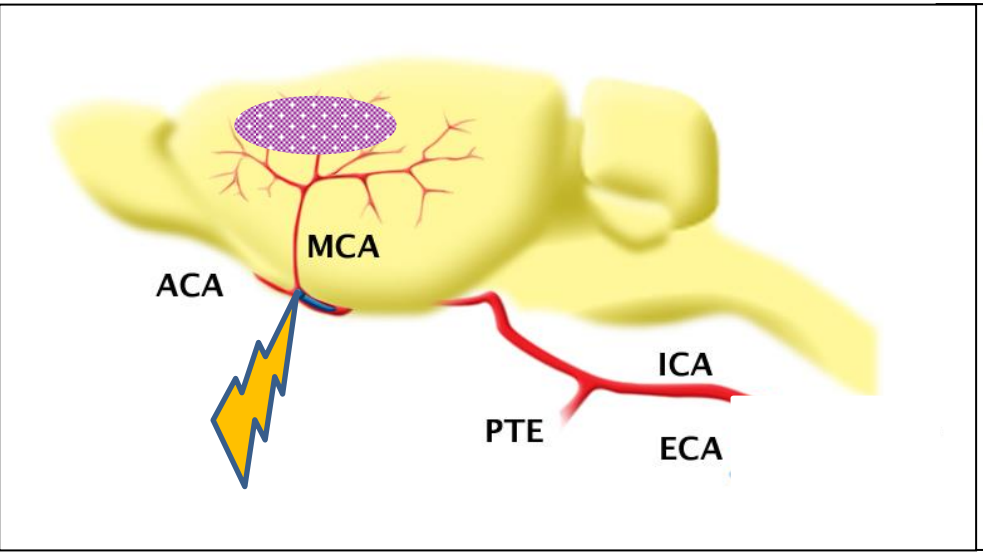


Question:

- What are the mechanisms of harm?

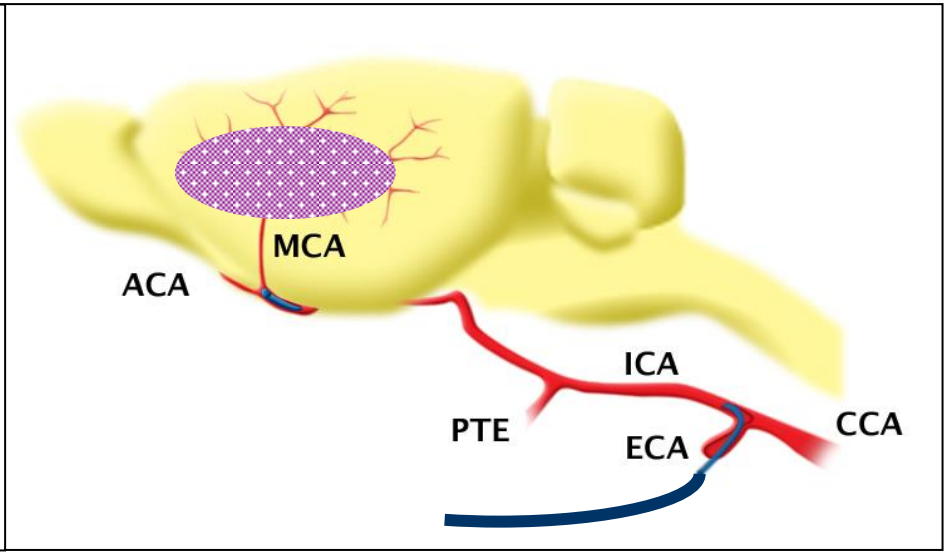
Rodent Models of Focal Cerebral Ischaemia

Permanent middle cerebral artery occlusion



Examine influences on penumbra

Transient middle cerebral artery occlusion



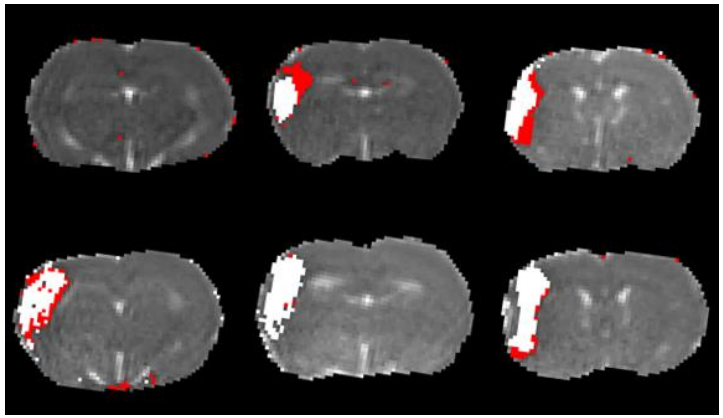
Examine influences on reperfused tissue

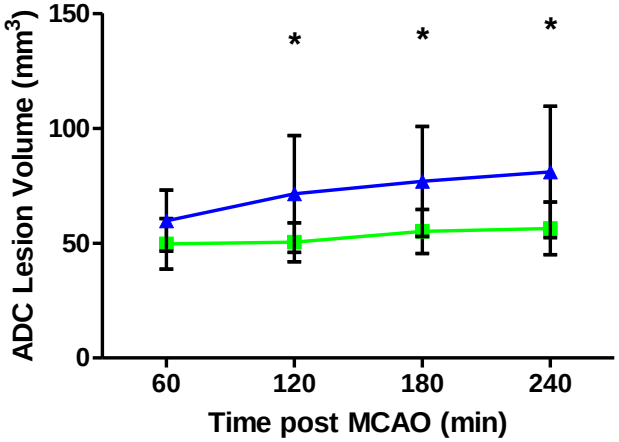
Hyperglycemia exacerbates ischaemic brain damage in rats

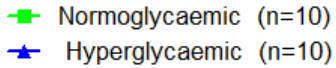
Early lesion growth by DWI MRI

Vehicle

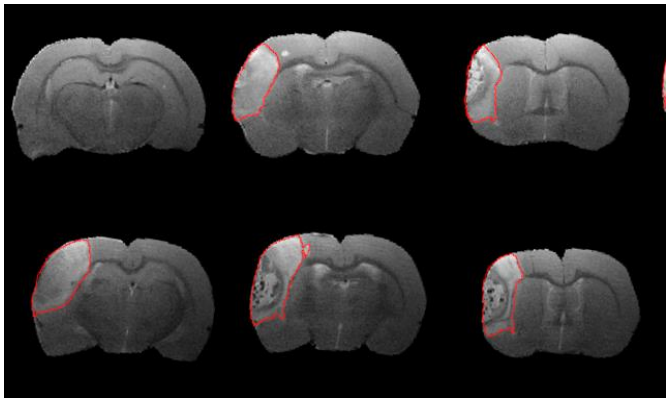
Glucose

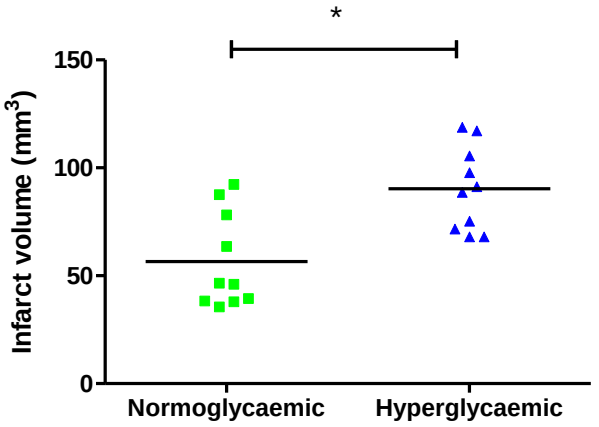




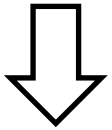


Infarct volume by T2 MRI (24h)





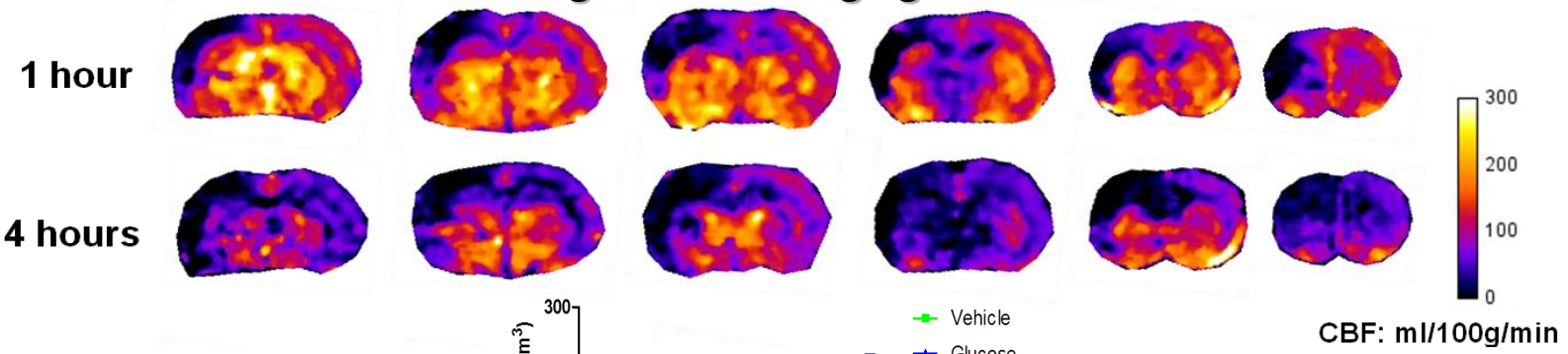
Roy et al, unpublished



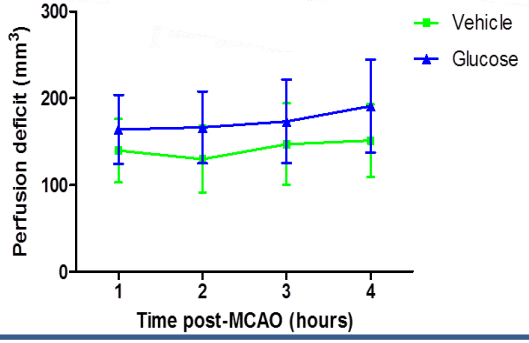
Is the increase tissue damage due to more severe reductions in CBF?

Hyperglycemia does not influence the severity of ischaemia

Perfusion-weighted MR imaging of CBF over time

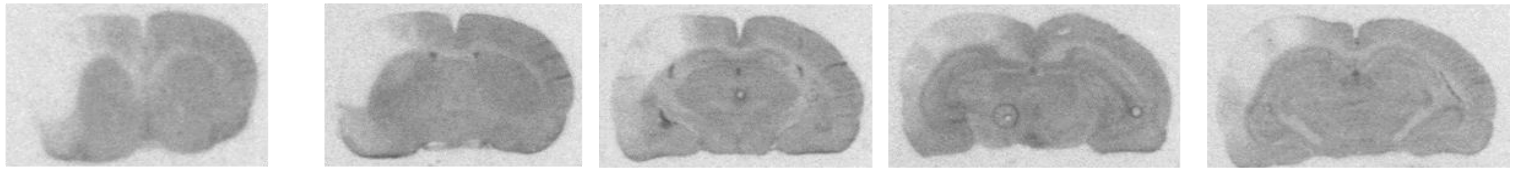


Tissue < 30 ml/100g/min

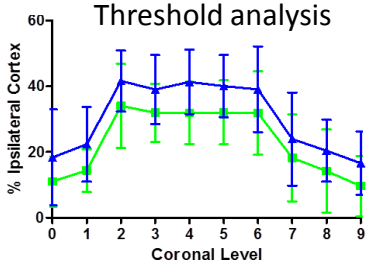


Roy et al, unpublished

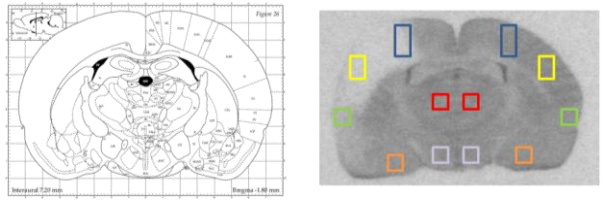
In vivo autoradiography of CBF – 1h after arterial occlusion



Threshold analysis



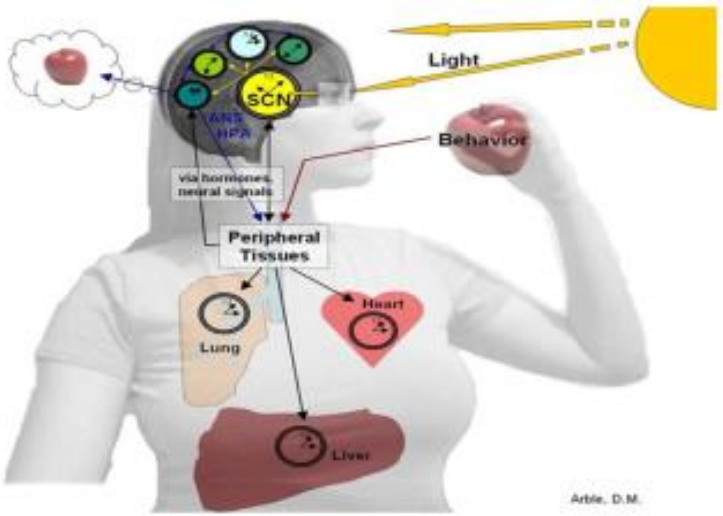
ROI analysis



Causes of post-stroke hyperglycaemia:

Stress response to the hypoxic insult

Undiagnosed disorder of glucose metabolism



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Circadian desynchrony and metabolic dysfunction; did light pollution make us fat?

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[b] Department of Psychology, National University of Ireland, Maynooth, Co Kildare, Ireland

- Circadian desynchrony occurs after jet-lag and shift work
- Associated with physiological changes that impact on stroke

e.g. hyperglycemia, hypertension, metabolic syndrome

Does circadian desynchrony adversely affect stroke outcome?

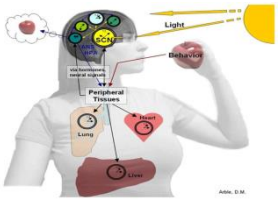
No effect of photoperiod disruption on vulnerability to focal cerebral ischaemia in rats

Ku Mastura Ku Mohd Noor[1], Lisa Roy[1], Cathy Wyse[2], Christopher McCabe[1], Deborah Dewar[1].

[1] Institute of Neuroscience & Psychology, College of Medical, Veterinary & Life Sciences, [2] Institute of Biodiversity, Animal Heath and Comparative Medicine, University of Glasgow, Scotland

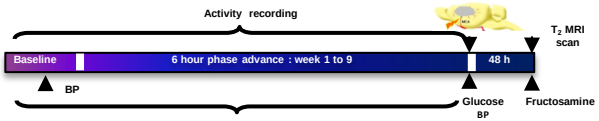
Background & Aims

- 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, hyperglycemia)[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, 1981[3]
- **MRI:** infarct volume was assessed by T_2-weighted MRI 48 h following MCAO by an experimenter

Results

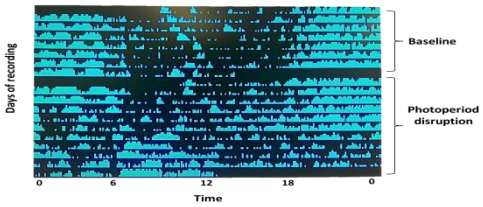


Figure 1. Double plotted actogram measured by cage-top movement sensors shows PD resulted in temporal dissociation between light/dark cycle and activity. Each horizontal line represents the day of recording, and total number of movements detected. Time of the day (hour) represented by x axis. At baseline, PD rats exhibited clear rhythms entrained to the light/dark cycle i.e. high activity during the dark phase.

Control and PD rats displayed comparable body weight gain and food intake

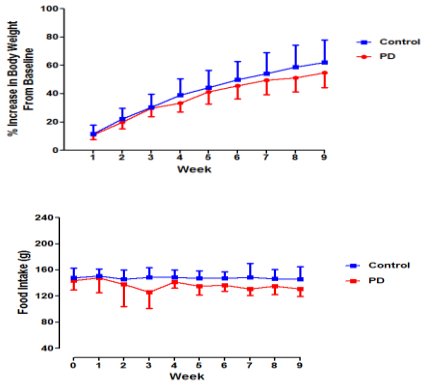


Figure 2. Two-way ANOVA with Bonferroni post test indicated that there was no significant difference in % of body weight gained and food intake between groups.
(P > 0.05, n=12). Data presented as mean ± SD.

Change in BP was not significantly different between groups

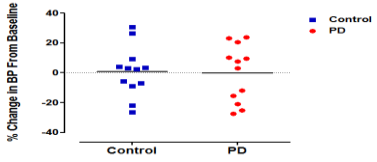


Figure 3. Percentage BP changes from baseline at the end of the 9 week period were not significantly different between groups. Data points indicate individual rats and horizontal bar represents the mean; unpaired t-test; P=0.89

PD had no effect on blood glucose immediately prior to MCAO

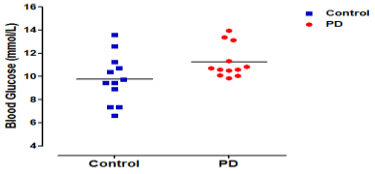


Figure 4. Blood glucose levels immediately prior to MCAO. Data points indicate individual rats and the horizontal bar represents the mean. Unpaired t-test revealed no significant different in blood glucose in PD rats compared to control immediately prior to MCAO (P=0.056)

No effect of PD on infarct size after permanent MCAO

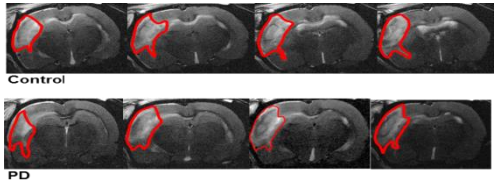


Figure 5. T_2-weighted MRI images obtained 48 h after MCAO showing infarcted areas as hyper intense regions outlined in red. Representative slices are from the median animal in control and PD groups.

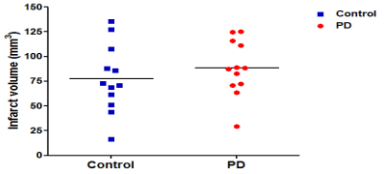


Figure 6. PD for 9 weeks did not exacerbate infarct volume. Data points indicate individual rats and the horizontal bar represents the mean; unpaired t-test; P=0.41

PD had no effect on plasma fructosamine level

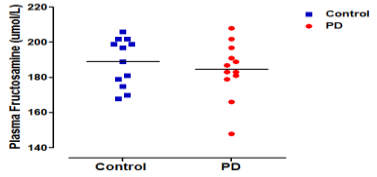


Figure 7. Plasma fructosamine level at 48 h after MCAO. Fructosamine levels reflect average glycaemic levels over the preceding 2-3 weeks prior to MCAO. Differences between groups are not statistically significant: unpaired t-test; P= 0.47

References.

[1] Gale, J.E. et al., 2011. Disruption of Circadian Rhythms Accelerates Development of Diabetes through Pancreatic Beta-Cell Loss and Dysfunction. Journal of biological rhythms, 26(5), pp.423–433.

[2] Kishi, T. & Sunagawa, K., 2011. Experimental "jet lag" causes sympathoexcitation via oxidative stress through AT1 receptor in the brainstem. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2011, pp.1969–72

[3] Tamura A, et al. 1981. Focal Cerebral Ischaemia in the Rat: 1. Description of Technique and Early Neuropathological Consequences Following Middle Cerebral Artery Occlusion. Journal of Cerebral Blood Flow and Metabolism 1: 53-60

Acknowledgement.

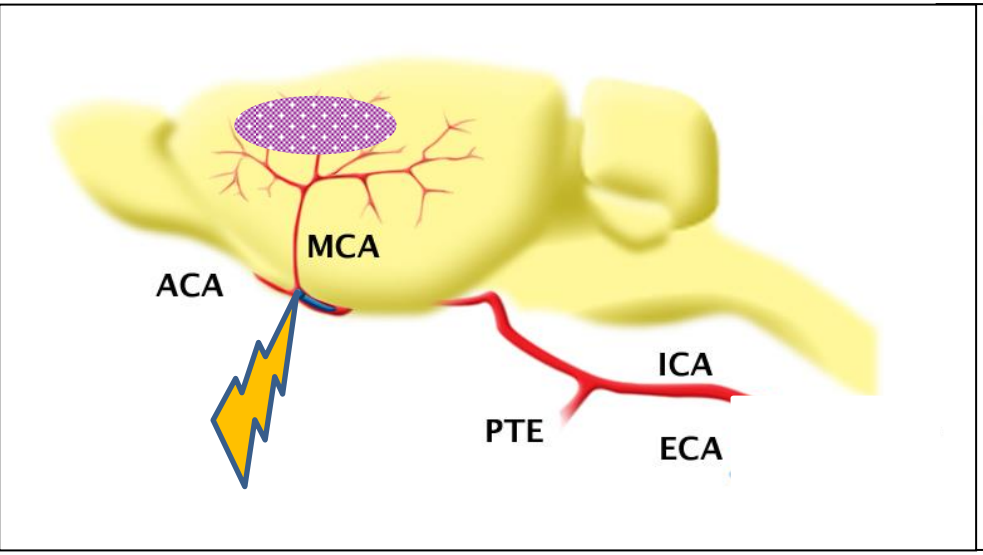
Supported by Ministry of Higher Education of Malaysia, and Islamic Science University of Malaysia.

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.

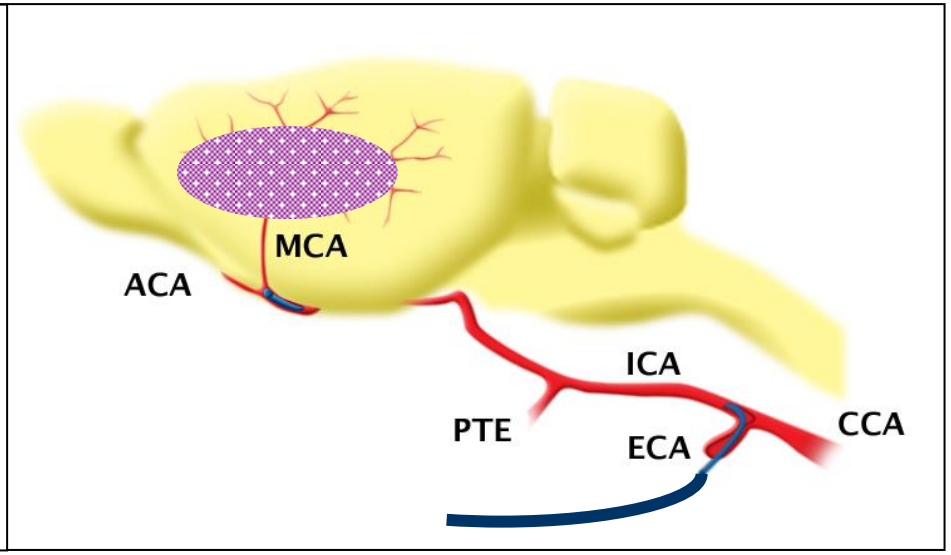
Rodent Models of Focal Cerebral Ischaemia

Permanent ischaemia



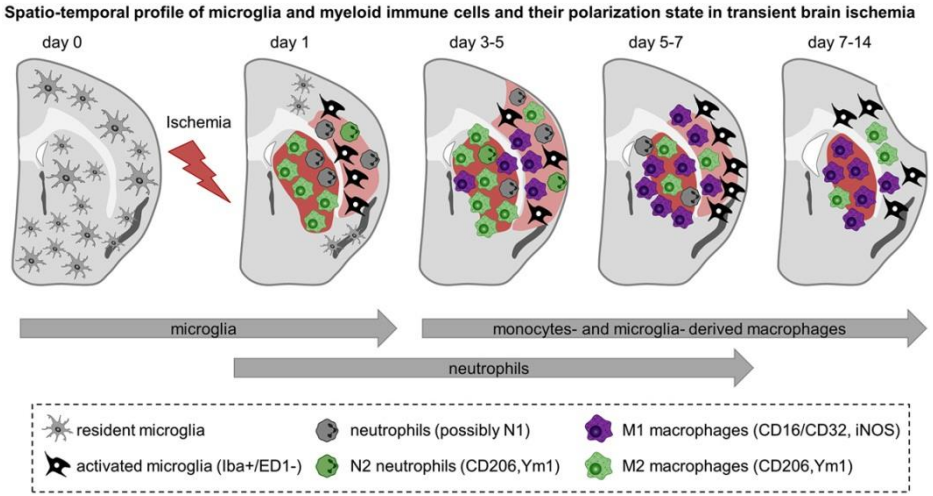
No effect of photoperiod disruption

Ischaemia with reperfusion



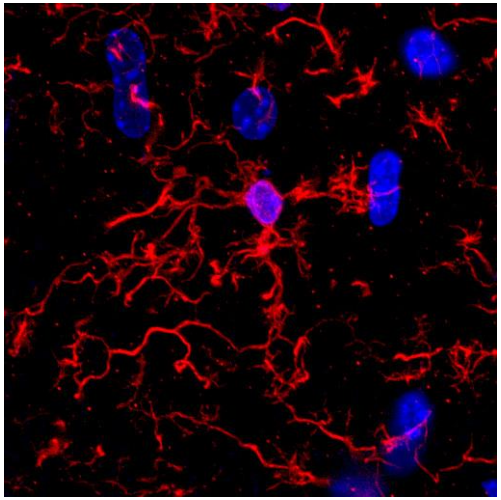
+ hypertension

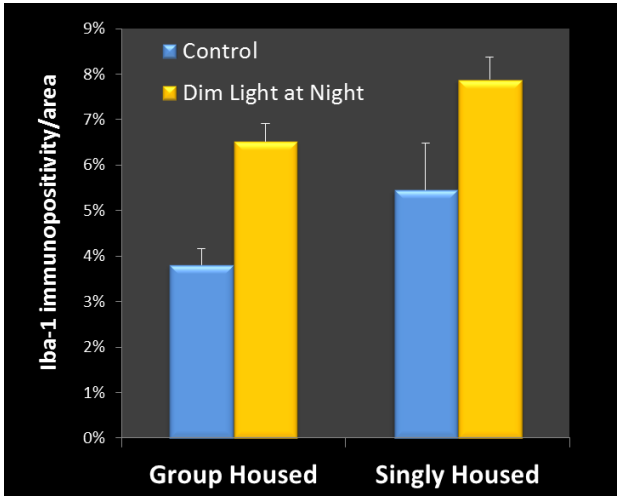
Immune response is major contributor to ischaemia + reperfusion pathobiology



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

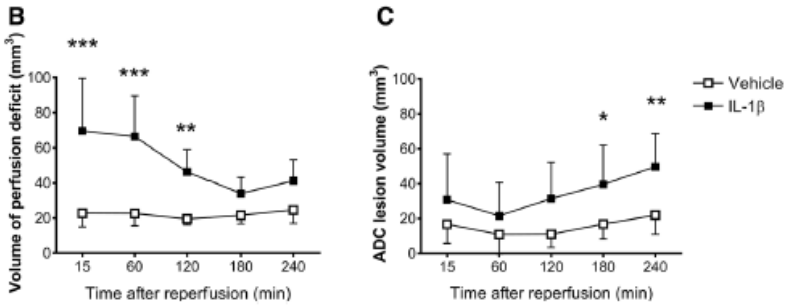
Does circadian desynchrony "prime" the immune system to exacerbate damage after ischaemia + reperfusion?

Vascular?

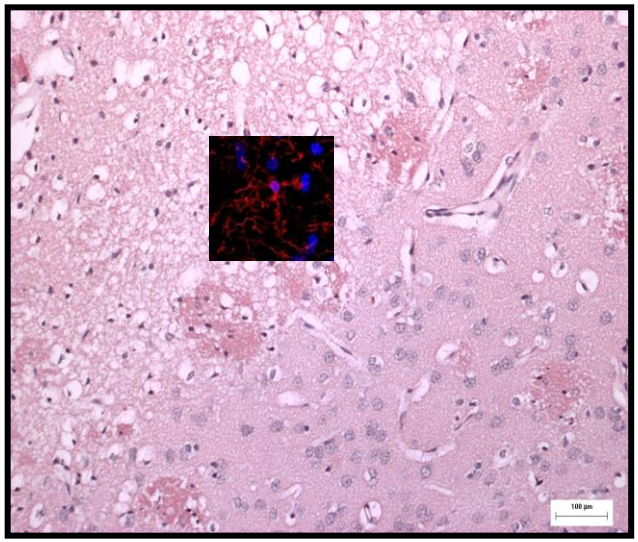
Parenchymal?

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

Katie N. Murray, BA (Hons); Sylvie Girard, PhD; William M. Holmes, PhD; Laura M. Parkes, PhD; Stephen R. Williams, PhD; Adrian R. Parry-Jones, PhD, MRCP; Stuart M. Allan, PhD



Stroke. 2014 45:3412-9



What do we need?

Immunology expertise and techniques for tissue/blood analysis