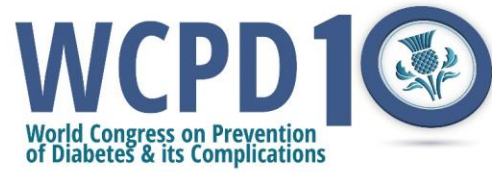




Basic science of prevention

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Nrf2-mediated protection against recurrent hypoglycaemia induced cognitive deficits in Type 1 diabetes

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Hypoglycaemia and cognitive function

- Hypoglycaemia the most common metabolic adverse effect of insulin therapy
- Acute hypoglycaemia (<3.0 mmol/l) causes cognitive dysfunction¹
- Profound hypoglycaemia (<1.0 mmol/l +/- seizures) results in neurological damage and persisting cognitive deficits^{2,3}
- In humans it is not known whether recurrent moderate hypoglycaemia has long term cognitive sequelae
- Studies limited by short duration, inability to accurately measure hypoglycaemia frequency

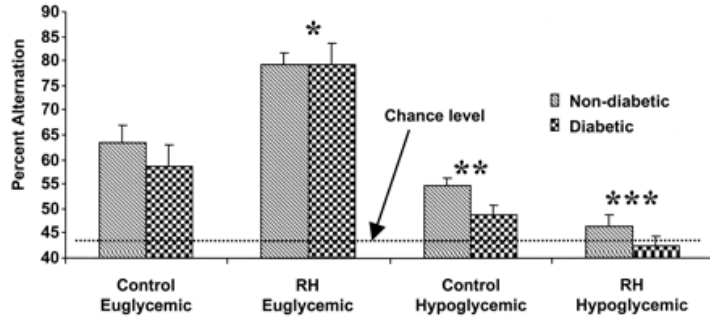
1 Graveling AJ et al Diabetes Care (2013) Oct;36(10):3240-46

2 Langan SJ et al Diabetologia (1991) 34(5):337-44

3 Won SJ et al J Neuroinflammation (2012) 25(9):182

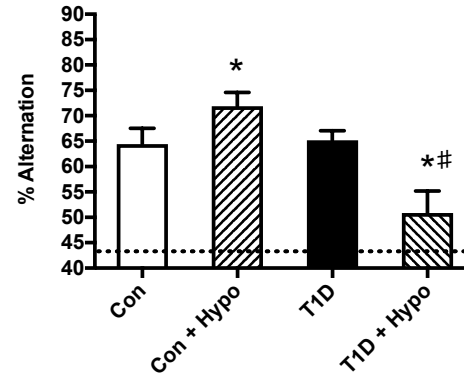
Recurrent hypoglycaemia and cognitive function

A) RH improves cognition



McNay EC & Sherwin RS 2004 Diabetes 53(2):418-425

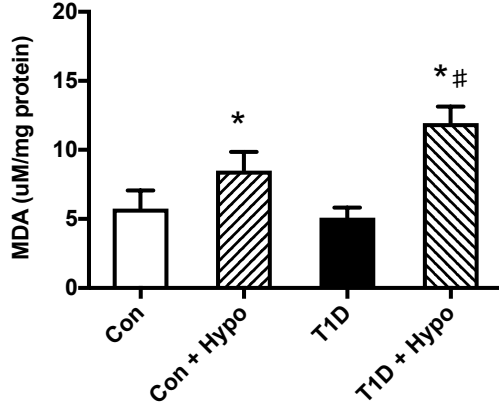
B) RH impairs cognition in T1D



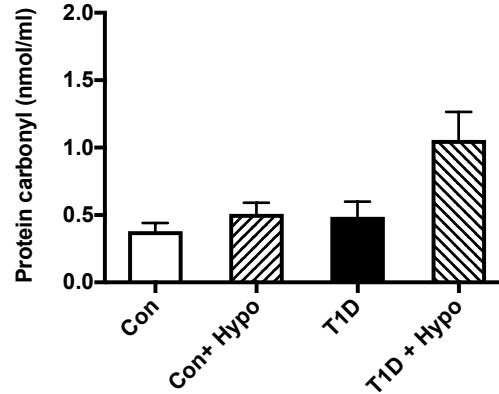
McNeilly AD et al 2016 Diabetes 65(10):3151-60

Oxidative stress and Nrf2

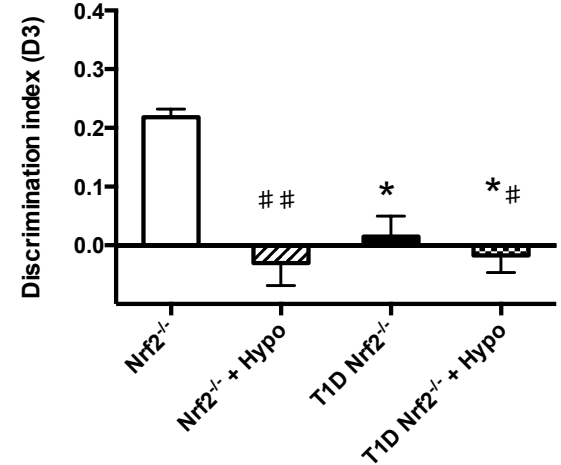
A) Lipid peroxidation



B) Protein carbonylation



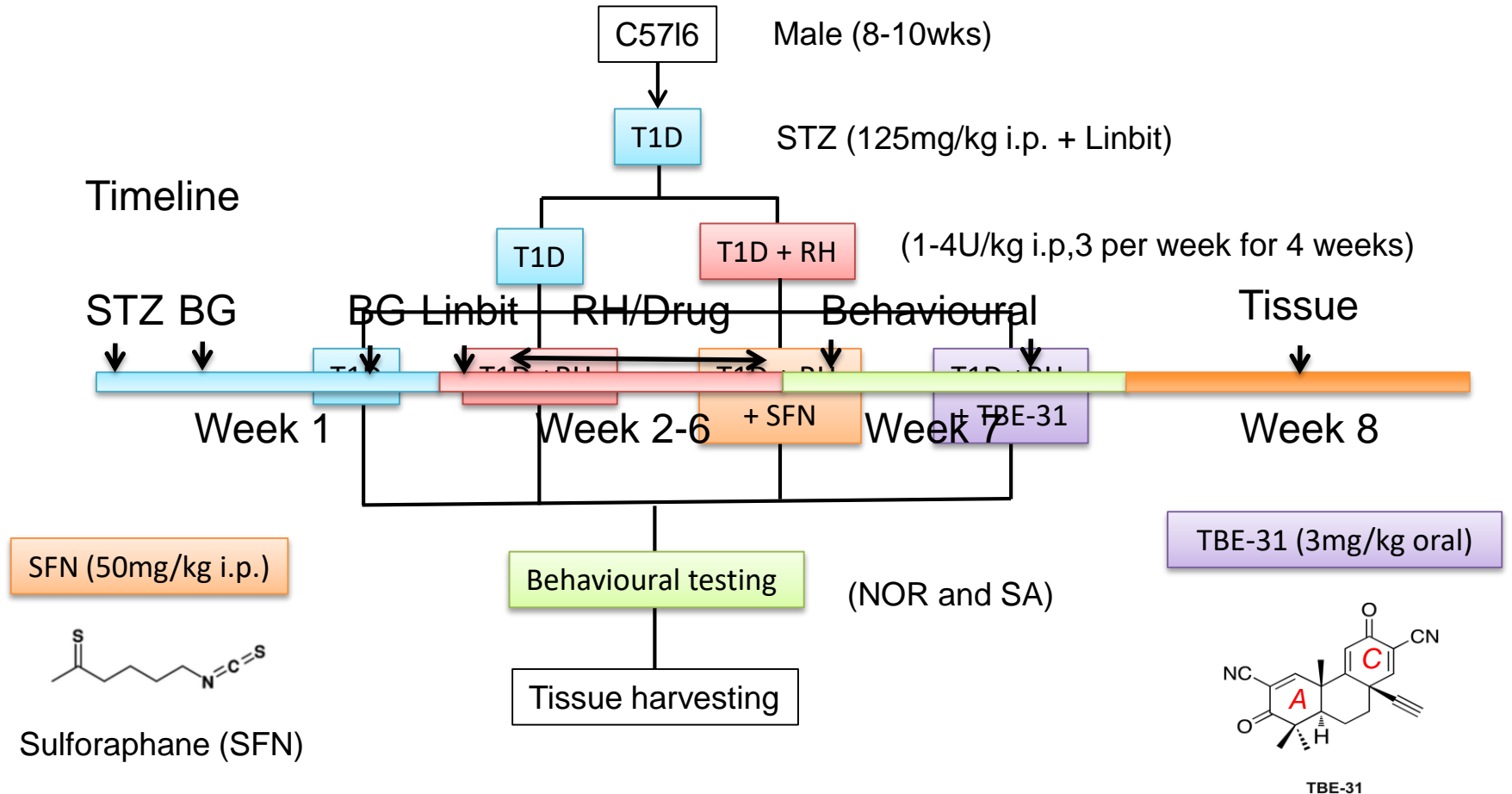
C) Nrf2 and cognition



Hypothesis

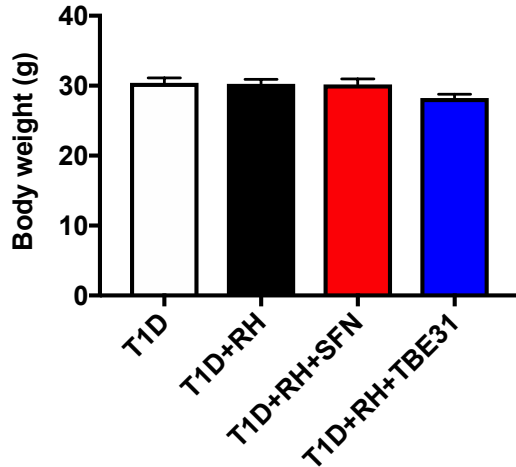
“Cognitive dysfunction associated with RH in T1D is mediated by redox imbalance – activation of Nrf2 pathway may alleviate these deficits”

Experimental design

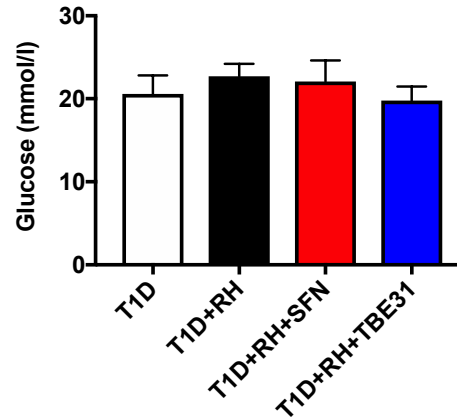


Supplementation has no impact upon body weight or FBG but reduces HbA1c

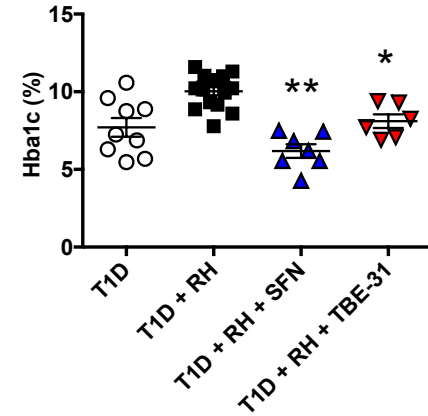
A) Body weight



B) Blood glucose



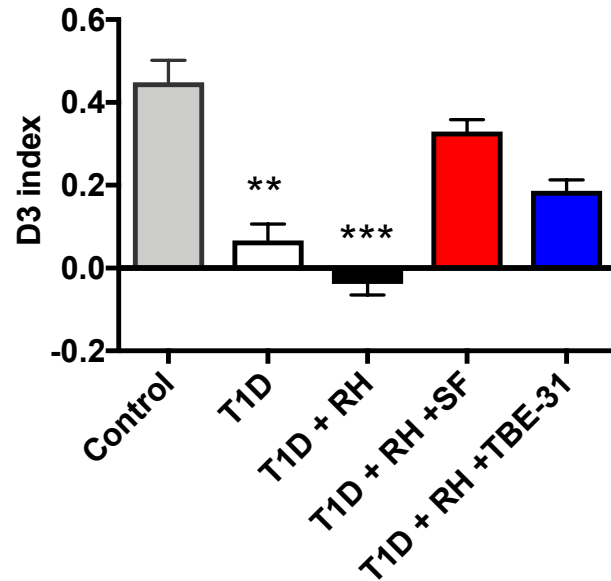
C) HbA1c



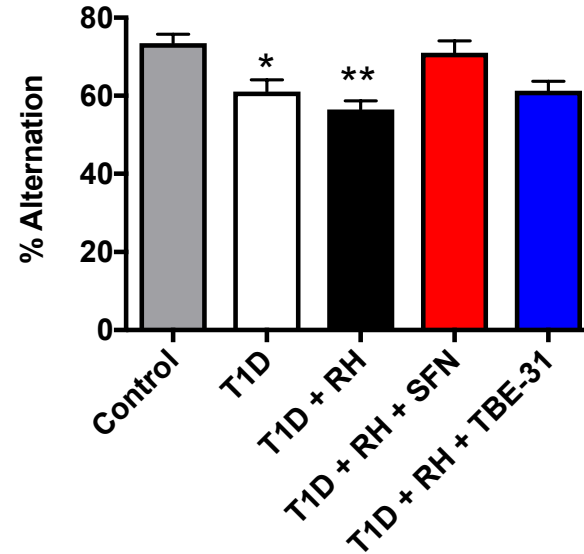
(n=8-10 per group; *p<0.05, **p<0.01)

Long-term memory and spatial working memory are restored by supplementation with SFN

A) Long term memory



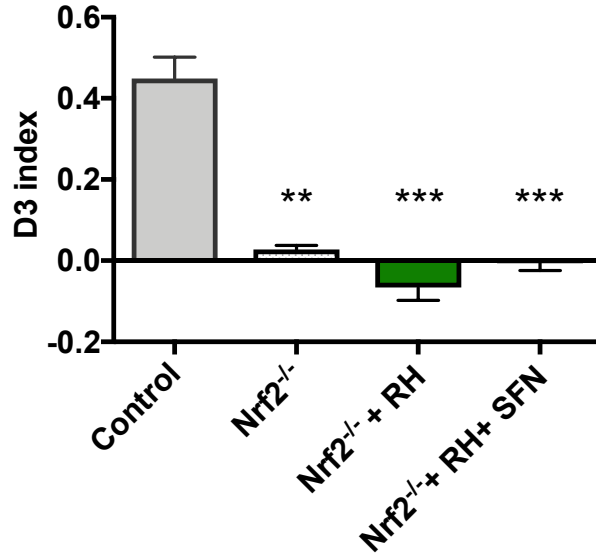
B) Spatial working memory



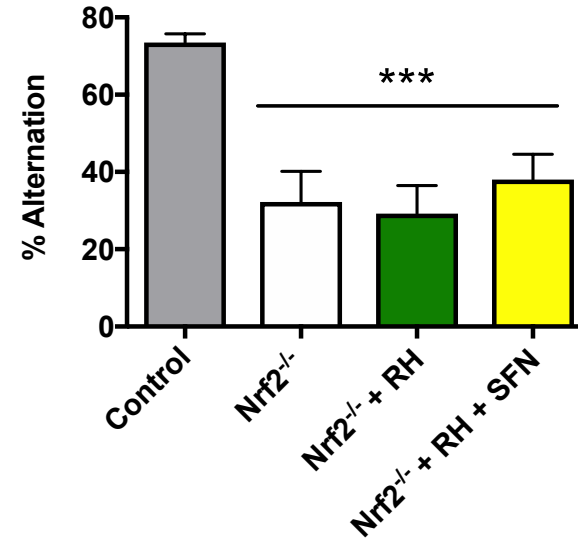
(n=8-10 per group; **p<0.01, ***p<0.001)

Improvements mediated via Nrf2 pathway

A) Long-term memory



B) Spatial working memory



(n=8-10 per group; **p<0.01, ***p<0.001 vs Control)

Summary

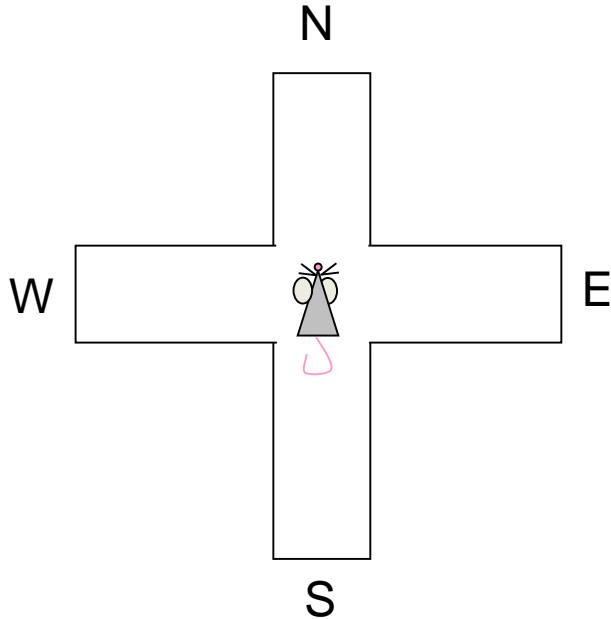
- The Nrf2 pathway offers protection against RH induced oxidative stress.
- Supplementation with SFN and/or TBE-31 significantly improves long-term memory and spatial working memory.
- HbA1c is significantly lowered with SFN
- Activation of the endogenous Nrf2 pathway offers a novel therapeutic target for cognitive dysfunction in T1D.

Acknowledgements

- Prof Rory McCrimmon
- Jennifer Gallagher
- Prof A Dinkova-Kostova
- All in McCrimmon lab

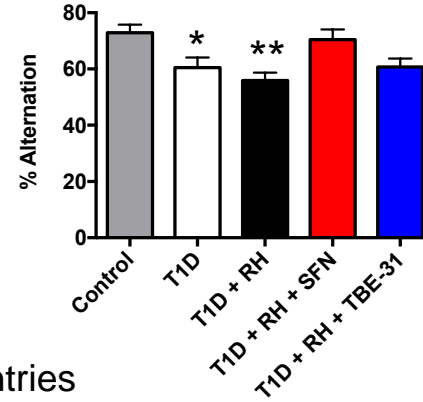
Spatial working memory is improved with SFN

Spontaneous alternation

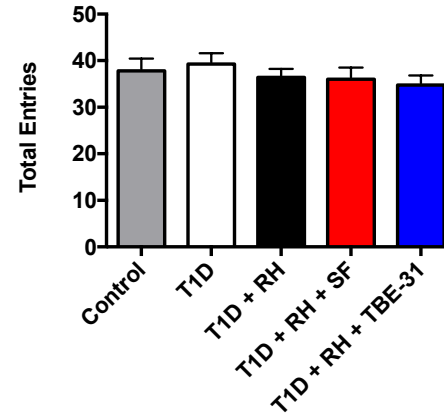


$$\% \text{ Alternations} = \frac{\text{Total no alternations}}{(\text{Total entries} - 4)}$$

% Alternation

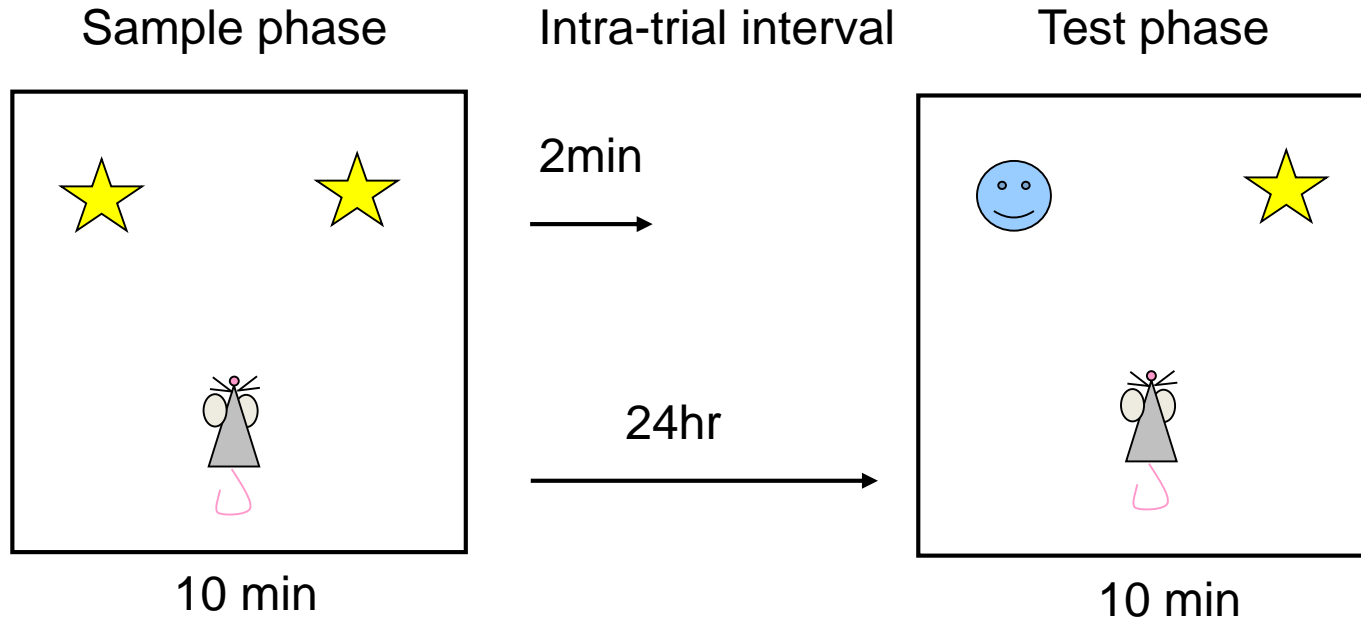


Total entries



Tests of cognitive function

- Novel Object Recognition



Nrf2 and Type 1 diabetes

Nrf2-Mediated Neuroprotection Against Recurrent Hypoglycemia Is Insufficient to Prevent Cognitive Impairment in a Rodent Model of Type 1 Diabetes
 Diabetes 2016 Oct; 65(10): 3151-3160.

