The Journal of Physiology

PERSPECTIVE

Back to the beginning: can we stop brain injury before it starts?

Joanne O. Davidson, Alistair J. Gunn and Justin M. Dean

Department of Physiology, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand

Email: j.dean@auckland.ac.nz

Edited by: Laura Bennet & Janna Morrison

Linked articles: This Perspective article highlights an article by Tran et al. To read this paper, visit https://doi.org/10.1113/JP282840.

The peer review history is available in the Supporting Information section of this article (https://doi.org/10.1113/JP283330#support-information-section).

Neonatal hypoxic–ischaemic encephalopathy (HIE) attributable to a lack of oxygen and reduced blood flow around the time of birth remains a major global problem, with more than a million associated deaths and 400,000 babies with brain injury every year, contributing to 2.4% of the total global burden of disease. Neonatal HIE affects approximately one to three infants per 1000 in high-income countries and ∼10 times more in low- to middle-income countries. We now know that in high-income countries, therapeutic hypothermia started within 6 h of birth significantly improves survival and reduces disability after HIE. However, nearly half of infants treated with therapeutic hypothermia die or survive with disability, although subsequent trials suggest that current protocols are near optimal. Crucially, the recent large, well-designed HELIX trial in low- to middle-income countries showed that therapeutic hypothermia did not improve outcomes after moderate-to-severe HIE (Thayyil et al., 2021).

A common element that might explain the lack of benefit of hypothermia for some infants with HIE is that hypoxia–ischaemia can start well before birth and can evolve for many hours over the course of labour. Thus, at the time of birth, in many cases the brain injury is no longer at a treatable stage. In this issue of *The Journal of Physiology*, Tran et al. (2022) propose that instead of trying to reduce brain injury by suppressing the evolution of established HIE, we should instead go back to the beginning and build up the defences of the brain against hypoxia–ischaemia before it occurs. Conceptually, if the intervention were to be sufficiently inexpensive and safe, it could be given even to low-risk mothers well before labour and thereby protect babies around the world.

In this study, the authors tested fetal creatine supplementation before hypoxic–ischaemic brain injury in near-term fetal sheep. Creatine is a simple guanidine compound abundantly expressed throughout the body, which is both synthesized endogenously and ingested in foods and is widely used as a sports and exercise supplement. Creatine and its phosphorylated form, phosphocreatine, act physiologically in vertebrates as an ATP buffer to maintain ATP-dependent cellular metabolism in all organs. After hypoxia–ischaemia, failure of brain oxidative energy metabolism is the central event initiating brain cell injury and cell death. Thus, creatine supplementation could increase the capacity to maintain cerebral mitochondrial ATP homeostasis during hypoxia–ischaemia. Furthermore, there is some evidence that creatine might have beneficial antioxidant actions.

In this study, fetal creatine supplementation (at doses that increased the total creatine content in the brain) reduced baseline brain pyruvate and glycerol concentrations (measured by brain microdialysis) and reduced cerebral hydroxyl radical efflux up to 24 h after hypoxia–ischaemia. Furthermore, fetuses with higher arterial creatine concentrations had smaller reductions in the arterial partial pressure of oxygen and oxygen saturation during hypoxia–ischaemia, and reduced cerebral pyruvate, lactate and hydroxyl radical accumulation after hypoxia–ischaemia. These findings suggest that prophylactic creatine supplementation allowed ATP turnover to be maintained for longer during hypoxaemia, thus reducing the requirement for mitochondrial oxidative phosphorylation and improving cerebral bioenergetics.

The reader should consider that in the present study, creatine treatment did not attenuate histological evidence of oxidative stress in the brain at 3 days after hypoxia–ischaemia. Furthermore, the extent of brain injury with prophylactic creatine treatment has not yet been assessed extensively in this or any other large animal translational model of perinatal hypoxia–ischaemia. Nevertheless, as recently reviewed (Tran et al., 2021), multiple preclinical rodent studies of perinatal hypoxic–ischaemic brain injury have shown neuroprotection with creatine supplementation. For example, maternal dietary creatine supplementation in spiny mice was associated with a profound reduction in apoptosis in the cortical subplate, piriform cortex and thalamus after birth asphyxia (Ireland et al., 2011). Administration of creatine both before and after hypoxia–ischaemia in postnatal day 7 rats was also associated with a significant increase in cerebral hemisphere volume and reduced neuronal necrosis in the cortex and hippocampus (see Tran et al., 2021).

An advantage of the proposed prophylactic creatine treatment strategy is that it might also protect other organs prone to injury after global hypoxia–ischaemia. For example, maternal creatine supplementation can reduce renal dysfunction in early adulthood after birth asphyxia in male spiny mice (Ellery et al., 2017). However, a limitation of this treatment strategy for clinical translation is that it might require a prolonged period of treatment before birth. Tran et al. (2022) gave creatine for 10 days before fetal hypoxia–ischaemia. It is unclear whether the same timing would be needed in humans. There might also be issues around compliance in women regularly taking, for a prolonged period of time, a treatment that might not be needed, and these difficulties might be amplified further in lower resource settings.

Overall, prophylactic creatine treatment shows promise for reducing HIE, most probably by increasing cerebral bioenergetics reserves. Although prophylactic treatment in pregnancy would be rather challenging, real-world examples of this approach include folic acid supplementation to prevent spinal defects and maternal magnesium sulphate administration before extremely preterm birth to reduce cerebral palsy. Future studies should use large animal translational models to quantify the impact of prophylactic creatine on brain injury in

DOI: 10.1113/JP283330

different models of hypoxia–ischaemia and, crucially, whether it can augment protection after current clinical protocols of therapeutic hypothermia.

References

Ellery, S. J., LaRosa, D. A., Cullen-McEwen, L. A., Brown, R. D., Snow, R. J., Walker, D. W., Kett, M. M., & Dickinson, H. (2017). Renal dysfunction in early adulthood following birth asphyxia in male spiny mice, and its amelioration by maternal creatine supplementation during pregnancy. *Pediatric Research*, **81**(4), 646–653.

Ireland, Z., Castillo-Melendez, M., Dickinson, H., Snow, R., & Walker, D. W. (2011). A maternal diet supplemented with creatine from mid-pregnancy protects the newborn spiny mouse brain from birth hypoxia. *Neuroscience*, **194**, 372–379.

Thayyil, S., Pant, S., Montaldo, P., Shukla, D., Oliveira, V., Ivain, P., Bassett, P., Swamy, R., Mendoza, J., Moreno-Morales, M., Lally, P. J., Benakappa, N., Bandiya, P., Shivarudhrappa, I., Somanna, J., Kantharajanna, U. B., Rajvanshi, A., Krishnappa, S., Joby, P. K., … Shankaran, S. (2021). Hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries (HELIX): A randomised controlled trial in India, Sri Lanka, and Bangladesh. *The Lancet Global Health*, **9**(9), e1273-e1285.

Tran, N. T., Kelly, S. B., Snow, R. J., Walker, D. W., Ellery, S. J., & Galinsky, R. (2021). Assessing creatine supplementation for neuroprotection against perinatal hypoxic-ischaemic encephalopathy: A systematic review of perinatal and adult pre-clinical studies. *Cells*, **10**(11), 2902.

Tran, N. T., Kowalski, G. M., Muccini, A. M., Nitsos, I., Hale, N., Snow, R. J., Walker, D. W., & Ellery, S. J. (2022). Creatine supplementation reduces the cerebral oxidative and metabolic stress responses to acute *in utero* hypoxia in the late-gestation fetal sheep. *Journal of Physiology*, **600**(13), 3193–3210.

Additional information

Competing interests

None.

Author contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

None.

Acknowledgements

Open access publishing facilitated by The University of Auckland, as part of the Wiley - The University of Auckland agreement via the Council of Australian University Librarians.

Keywords

brain injury, creatine, hypoxia–ischaemia, oxidative stress

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History