Changes in cerebral glucose metabolism in chemotherapy-induced cognitive impairment

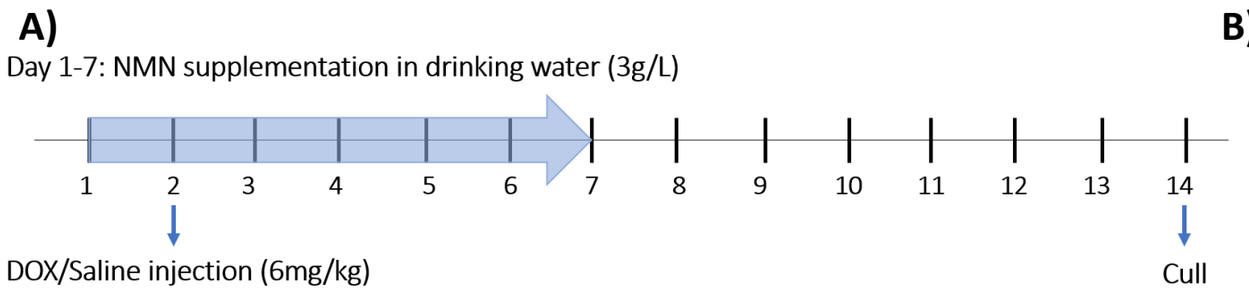
Catherine Li[1], Emily Si[2], Ian Johnston[2], Nicole Jones[1], Caroline Rae[3], David A. Sinclair[1,4] and Lindsay E. Wu[1]

[1]School of Medical Sciences, The University of New South Wales, Australia; [2]School of Psychology, The University of Sydney, Australia;
[3]Neuroscience Research Australia; [4]Department of Genetics, Harvard Medical School, USA

INTRODUCTION

Cancer survival has improved due to new treatment regimens, with the use of chemotherapy leading to a population of patients experiencing chemotherapy-induced cognitive impairments (CICI) that persist after cessation of chemotherapy, for which currently there are no available treatments. Chemotherapy drugs such as doxorubicin (DOX) induce DNA damage, which activates enzymes that consume nicotinamide adenine dinucleotide (NAD^+), a vital metabolite required for a range of important processes such as DNA repair and glucose metabolism. We speculated that DOX treatment may cause changes in glucose metabolism in the brain therefore causing CICI, and to address this we tested the ability of the NAD^+ precursor nicotinamide mononucleotide (NMN) to prevent this. This study aims to investigate the metabolic changes induced by DOX and the effects of NMN on glucose metabolism using ^1H and ^{13}C nuclear magnetic resonance spectroscopy.

METHODS



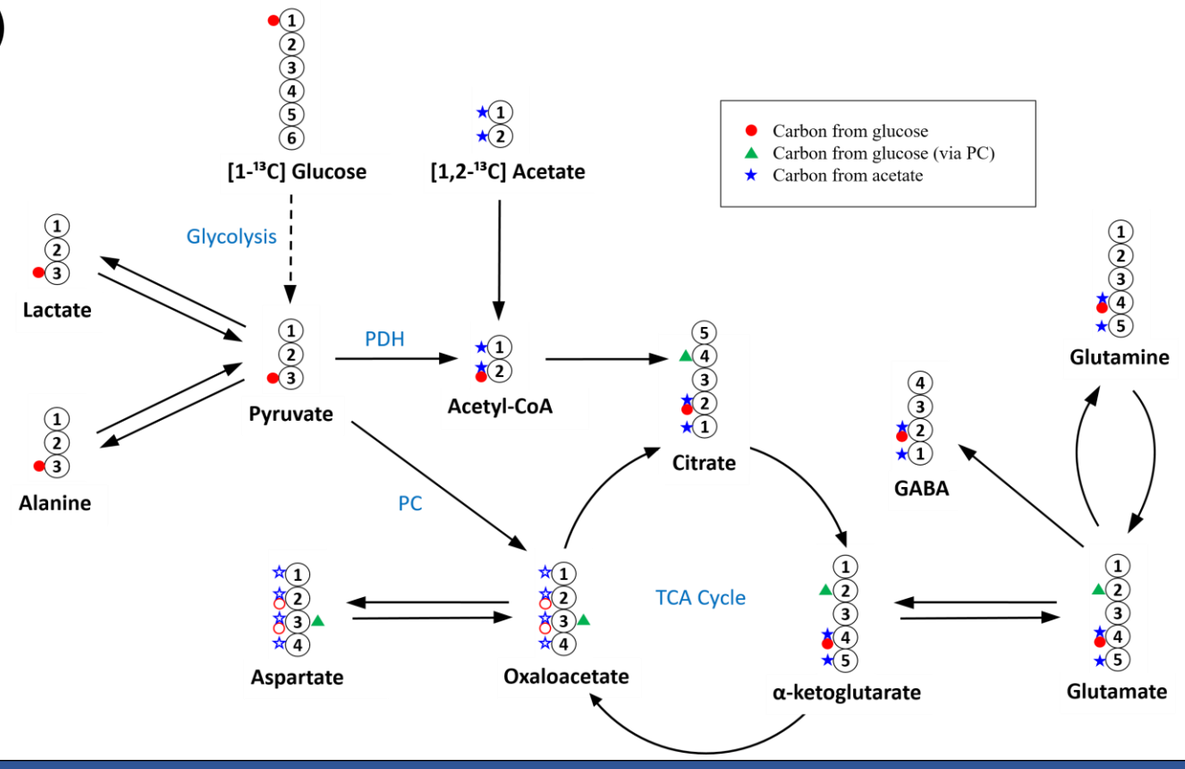
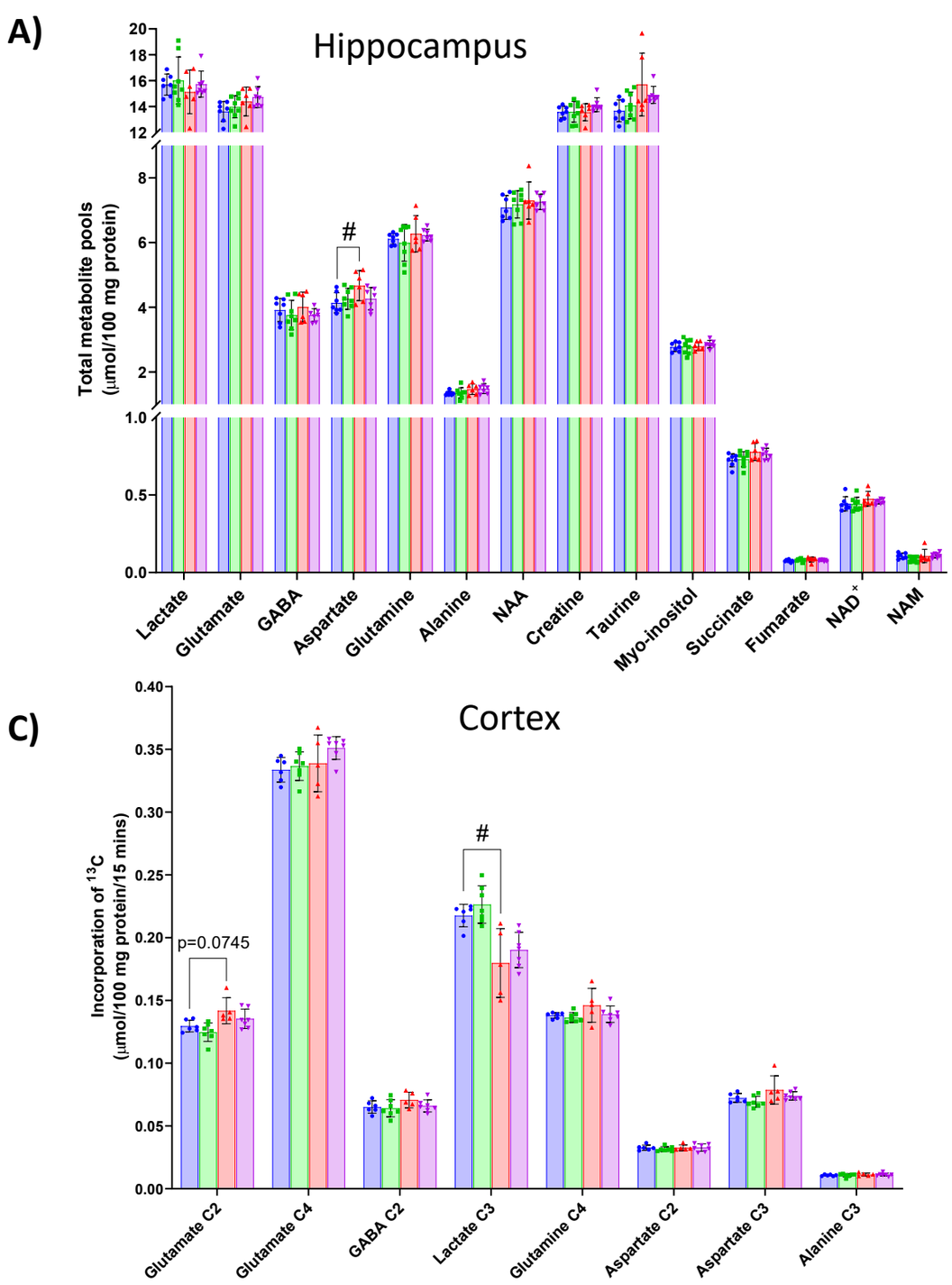


Figure 1. (A) Timeline of experimental procedure. Five-month-old C57BL6 male were treated according to the timeline above and sacrificed 12 days after DOX injection. On the day of the cull, mice were injected intraperitoneally with [1-13C] glucose (543 mg/kg, 0.3 M solution) plus [1,2-13C] acetate (504 mg/kg, 0.6 M solution), fifteen minutes prior to culling. The cortex and hippocampus were extracted and prepared for ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy. **(B)** Distribution of ^{13}C labelling following glucose and acetate metabolism. Abbreviations: PDH, pyruvate dehydrogenase; PC, pyruvate carboxylase.

RESULTS



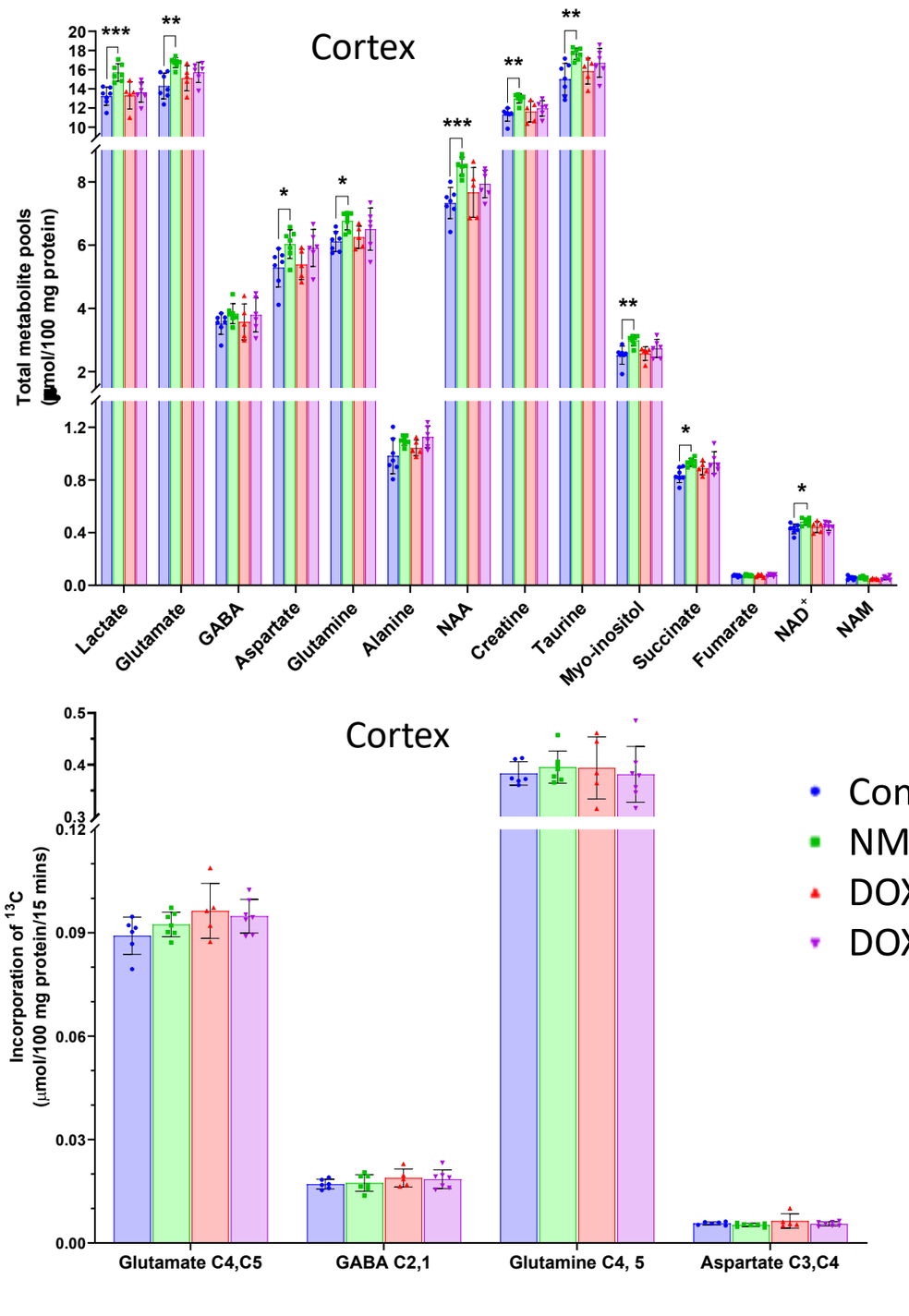


Figure 2. Proton spectroscopic quantification of total metabolic pool size in the **(A)** hippocampus and **(B)** cortex in DOX and NMN treated mice (n=5-8). Carbon spectroscopic quantification of **(C)** glucose and **(D)** acetate utilisation in the cortices of DOX and NMN treated mice (n=5-7). Data are expressed as mean ± SD. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, control vs NMN, and # $p < 0.05$ control vs DOX, using Kruskal-Wallis test following by Dunn's post hoc test.

CONCLUSION

These findings suggest that DOX may disrupt cerebral glucose metabolism by potentially increasing oxidative phosphorylation as a compensatory mechanism. Co-treatment with NMN did not rescue this effect, however, NMN alone may be able to increase cerebral blood flow. Further experiments are needed to verify these findings.