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Understanding the Vulnerability of Brain Cells to Ischaemia and Aging

As we live longer lives, it is critically important that we find explanations for the susceptibility of brain cells to injury. We have known for almost 100 years that some cells are much more sensitive to injury than others; it has always been the hope that understanding this selective vulnerability would lead to an understanding of mechanisms of cell death that might be tractable and become targets that would, if the right interventions were deployed, increase the tolerance of brain cells to the aging process.

Critically important to memory and personality is a well-functioning hippocampus. Within the hippocampus, highly connected groups of cells, so-called CA-1 to CA-4, express different vulnerabilities. These cells have been discovered to be the most sensitive cells in the brain; and in particular, those in the CA-1 sector, while being the most highly connected to CA-3, the dentate gyrus and the cortex, are extremely susceptible, whereas CA-3 are the most resistant. Following ischaemia, as a result of aging as a result of epilepsy, the interconnections are easily lost, and my thinking relates to the selective deafferentation and loss of interconnections that might influence cellular vulnerability.

The only thing we can currently do for patients to stop brain cells dying in the face of adversity is by changing temperature (such as cooling); this changes the susceptibility of brain cells, prevents them from dying and allows them to recover following a toxic insult. By changing metabolism and up-regulating mechanisms that utilize high cerebral metabolic rates, we can change the susceptibility of brain cells to ischaemia, and this has implications for the acute treatment of stroke and the prevention of dementia. Techniques that will be engineered to reduce energy demands will, if deployed in acute situations, allow us to protect the brain during stroke injury and help the brain cells to recover during stroke intervention with endogenous neuroprotection. It is hoped that, if we can extrapolate from these observations, we can find ways to sustain cells in more chronic neurodegenerative situations such as in Alzheimer's disease, dementia and neurodegenerative conditions. There is now a need to define specific criteria that will be much more predictive of true reproducibility to avoid unconscious bias, in order to predict what should go forward for effective clinical trials.

Recommended Reading

Attwell, D., A. M. Buchan, S. Charkpak, M. Lauritzen, B. MacVicar, and E. Neuman (2010). "Glial and neuronal control of brain blood flow." *Nature* 468: 233-244.

Papadakis, M., G. Hadley, M. Xilouri, L. C. Hoyte, S. Nagel, G. Tsaknakis, S. M. Watt, C. W. Drakesmith, R. Chen, Z. Zhao, B. Kessler, K. Vekrellis, and A. M. Buchan (2013). "Tsc1 (hamartin) confers neuroprotection against ischemia by inducing autophagy." *Nature Medicine* 19, 3: 351-357.

Neuhaus, A. A., Y. Couch, G. Hadley, and A. M. Buchan (2017). "Neuroprotection in stroke: the importance of collaboration and reproducibility." *Brain* 140, 8: 2079-2092.

Stroke: Lessons for Scientific Reproducibility and Clinical Translation

When I began my clinical practice in 1980, there were no treatments for stroke, a medical condition that will affect more than 1 in 4 people during their lifetime.

In the early 1980's, we explored the use of brain imaging, which for the first time allowed us to see what was actually happening to the brain, in real time, during an acute stroke. Combining both arterial and brain imaging allowed us to differentiate the various causes of stroke: cerebral hemorrhage (apoplexy), blockages of small penetrating blood vessels and occluded large vessels as a result of embolism, which akin to a heart attack, became known as a brain attack.

In the late 1980s we began to develop treatments, adapted from cardiology's treatment of heart attack, to open these occluded large arteries and restore blood flow to the brain. Imaging allowed us to quantify, stratify and select patients for appropriate intervention. Subsequent trial methodology allowed evidence-based medicine to demonstrate not only safety but also highly significant efficacy in a reproducible and accurate way.

While we have been successful with the restoration of blood flow to the brain, much of my recent experimental work has been in developing agents that protect brain-cells to reduce brain injury and buy more time to effect successful treatment in the wake of an acute stroke. Our problem has been with the unbridled enthusiasm of the proponents of various hypotheses, a lack of proof of concept studies, and a failure to translate and generate clinically effective therapies.

In my presentation, I will focus on the lack of experimental physiological control, critical analysis and the reproducibility of the accumulated data initially derived from models, and then show how and why these prototype agents failed in clinical trials. On a more upbeat note, I will show that effective methods to preserve brain-cell function can make our brains less susceptible to stroke. We are using observations on the brain cells in the hippocampus, some of which were originally described by Santiago Ramón y Cajal in the late 19th century, to understand how certain kinds of neuronal cells survive when others die. This approach, which I have termed endogenous neuroprotection, could be developed, and would be almost analogous to developing a vaccine, to protect the human brain at risk from the restriction of blood supply to the brain as we age.

It is my hope that in the questions and discussion, we can move on from what has been successful, reproducible and translatable, and analyze how experimental data, the exaggerated claims, and the lack of responsibility by investigators, funding agencies, publishing houses, institutions and industry have led to bad science, bad medicine and bad public policy. To be sure, some of the difficulties we have had with stroke research over 40 years can be compared with some of the knee-jerk responses during these initial, 4 months of the 2019-20 COVID-19 pandemic.

Above and beyond a discussion of stroke and ageing, my aspiration for the colloquium is to explore how we can achieve accountability, accuracy and reproducibility in making scientific claims. How should we ensure that there is adequate scrutiny of data and preliminary inferences to preclude the dissemination of flawed assertions and advice that have a negative impact on public health policy, increasing rather than decreasing risks to society and to the freedoms we hold so dear?

PUBLICATIONS FROM THE FELLOW LIBRARY

Buchan, Alastair M. (New York, NY, 2020)

Functional neurological disorder

<https://kxp.k10plus.de/DB=9.663/PPNSET?PPN=1725498634>

Buchan, Alastair M. (Oxford, 2017)

Neuroprotection in stroke : the importance of collaboration and reproducibility

<https://kxp.k10plus.de/DB=9.663/PPNSET?PPN=1668698706>

Buchan, Alastair M. (London, 2015)

Robust research : institutions must do their part for reproducibility

<https://kxp.k10plus.de/DB=9.663/PPNSET?PPN=1668698072>

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Capillary pericytes regulate cerebral blood flow in health and disease

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Buchan, Alastair M. (Seoul, 2013)

Endogenous neuroprotection : Hamartin modulates an austere approach to staying alive in a recession

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Tsc1 (hamartin) confers neuroprotection against ischemia by inducing autophagy

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Glial and neuronal control of brain blood flow

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