Feature Article Commentary

The Whole and The Parts, Development and Aging, Life and Death

Oscar Herreras

*Instituto Cajal – CSIC, Avda. Doctor Arce 37, Madrid, Spain**Journal of Cerebral Blood Flow & Metabolism* (2011) **31**, 994–995; doi:10.1038/jcbfm.2010.218; published online 22 December 2010

The involvement of anoxia/ischemia (AI) in neuropathology is more extensive than previously thought. The variety of insults extends from cardiac arrest to imperceptible microinfarcts. How these affect the nervous tissue is an arduous problem, in part due to the experimental tendency to focus on the parts instead of the whole. Over the years, this strategy taught us that white matter (WM) is far more resistant to AI than gray matter (Tekkok *et al*, 2003), and that astrocytes are more resistant than neurons (Sochocka *et al*, 1994), which work under an exquisite aerobic regime. Also, within neurons, the axon has its own energy factory and survives better than its parent soma, but peripheral axons are far more resistant than central fibers. That being said, the pieces have helped little in understanding the whole, i.e. how AI affects tissues made up of several metabolically coupled cell types, each with its own anaerobic capacity. For instance, selective disruption of the aerobic metabolism in astrocytes in intact normoxic tissue kills neurons (Largo *et al*, 1996). Also, different portions of the same axonal fibers travelling within central or peripheral tracts show strikingly varied resistance to AI (Utzschneider *et al*, 1991). Although calcium overload may be a common point in the road to irreversible injury (Kristián and Siesjö, 1998), the different cell types and elements may get there through diverse routes according to their own molecular machinery and/or the global properties of the tissue in which they are integrated. Selective vulnerability (Somjen *et al*, 1990) reminds us of the importance of supracellular factors in AI.

Indeed, brain energy metabolism is a case where dissecting the system for study downgrades the functions of its components. But, as is usual in life systems, this problem also has an additional dimension. There is a continuous remodeling from birth to aging (Boumezbeur *et al*, 2010). The article by Hamner *et al* (2011) brings us to a new standpoint.

By using portions of the optic nerve subjected to anoxia, the authors report total loss of electrogenesis in 8-month-old mice, but only partial in 1-month specimens. They propose a reduced anaerobic capacity of WM with age. The anoxic inactivation of axons in gray matter has internal (ATP exhaustion) and external challengers (depolarization driven by external potassium flood), although the latter may not be at play in peripheral axons and to different degrees in different central nerve tracts in WM. The interesting point in Hamner's report is that it calls our attention to a poorly attended issue: axonal metabolism may also change with age. As the experiments were carried out in mice, we do not know yet how much this finding may relate to development or to aging in humans. New opportunities emerge for the clinics. In neurodegenerative brain diseases, we should start considering the possibility that axons may be as labile as cell bodies when facing AI episodes. For instance, microinfarcts might produce axonal damage, which may lead to neurological deficits as much as soma damage.

Disclosure/conflict of interest

The authors declare no conflict of interest.

References

- Boumezbeur F, Mason GF, de Graaf RA, Behar KL, Cline GW, Shulman GI, Rothman DL, Petersen KF (2010) Altered brain mitochondrial metabolism in healthy aging as assessed by *in vivo* magnetic resonance spectroscopy. *J Cereb Blood Flow Metab* 30:211–21
- Hamner MA, Möller T, Ransom BR (2010) Anaerobic function of CNS white matter declines with age. *J Cereb Blood Flow Metab* 31:996–1002 (this issue)
- Largo C, Cuevas P, Somjen GG, Martín del Río R, Herreras O (1996) The effect of depressing glial function in rat brain *in situ* on ion homeostasis, synaptic transmission, and neuron survival. *J Neurosci* 16:1219–29
- Kristián T, Siesjö BK (1998) Calcium in ischemic cell death. *Stroke* 29:705–18
- Sochocka E, Juurlink BH, Code WE, Hertz V, Peng L, Hertz L (1994) Cell death in primary cultures of mouse

Correspondence: Dr O Herreras, Instituto Cajal – CSIC, Avda. Doctor Arce 37, Madrid 28002, Spain.

E-mail: herreras@cajal.csic.es

Received 18 November 2010; accepted 18 November 2010; published online 22 December 2010

- neurons and astrocytes during exposure to and 'recovery' from hypoxia, substrate deprivation and simulated ischemia. *Brain Res* 638:21–8
- Somjen GG, Aitken PG, Balestrino M, Herreras O, Kawasaki K (1990) Spreading depression-like depolarization and selective vulnerability of neurons. A brief review. *Stroke* 21(Suppl III):179–83
- Tekkok SB, Brown AM, Ransom BR (2003) Axon function persists during anoxia in mammalian white matter. *J Cereb Blood Flow Metab* 23:1340–7
- Utzschneider DA, Kocsis JD, Waxman SG (1991) Differential sensitivity to hypoxia of the peripheral versus central trajectory of primary afferent axons. *Brain Res* 551:136–41