replication more effectively than cells from patients with LHON. Collectively, these findings indicate that mitochondrial mass increases in response to LHON mutations and large increases may be protective in asymptomatic carriers. Presumably, the increased amount of mitochondrial compensates for the defect of respiratory chain complex I in the patients.

Although this excellent translational research study by Giordano et al. (2014) strongly supports the notion that mitochondrial biogenesis is protective in LHON, proof of this concept will require identification of the factor(s) responsible for activating mitochondrial proliferation and experimental manipulation of the biogenesis factors in cells and animal models. If validated and extended, these observations will have clinical diagnostic and therapeutic implications, as noted by the authors. For example, they note that levels of mitochondrial DNA in white blood cells of LHON mutation carriers may prove to be a biomarker predictive of developing blindness. Identification of the pathway responsible for mitochondrial DNA biogenesis will provide a pharmacological target to prevent blindness. Identification of the pathway responsible for mitochondrial DNA biogenesis will provide a pharmacological target to prevent blindness in unaffected mutation carriers. Studies have already demonstrated promising therapeutic effects of activating mitochondrial biogenesis in mouse models of mitochondrial diseases with defects of the respiratory chain (Wenz et al., 2008; Viscomi et al., 2011). Remarkably, Giordano et al. have shown that asymptomatic LHON mutation carriers may already be taking advantage of enhancing mitochondrial mass to prevent blindness.

Michio Hirano, MD
Columbia University Medical Centre
New York, NY USA
E-mail: mh29@cumc.columbia.edu
doi:10.1093/brain/awu005

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Syncope: how the EEG helps in understanding clinical findings

Although it is now widely accepted that the key to accurate diagnosis and risk stratification of syncope is a thoughtful and scrupulous history, exactly what is meant by the history remains unclear, and moving it from experts to front-line workers has proven difficult. Partly this is because syncope is simply a symptom, like fever, with a plethora of potential causes. Partly as well this reflects the multitude of somewhat overlapping symptoms and signs for the most common form, the ‘faint’ or vasovagal syncope. There are several clinical features that are known to be helpful in the differential diagnosis of loss of consciousness, based on quantitative symptom studies. These for example help distinguish epileptic convulsions and pseudosyncope from syncope, but such studies were aimed at clinical decision-making. They reported just the most highly significant clinical points and do not help clinicians make sense of the worder of symptoms that clinical experience suggests (Sheldon et al., 2002, 2006; Wieling et al., 2009; Tannemaat et al., 2013).

In this issue of Brain, van Dijk et al. (2014) provide fascinating and informative insights into why some symptoms cluster with each other in patients with vasovagal syncope. The authors performed detailed EEG and videometric analyses of 69 patients with positive responses to head-up tilt table testing. The EEG provides an objective marker of brain dysfunction during the cerebral hypoperfusion that accompanies syncope. For nearly 60 years investigators have described EEG patterns during provoked reflex syncope (Gastaut and Fischer-Williams, 1957; Ammirati et al., 1998; Sheldon et al., 1998; Martinez-Fernandez et al., 2008). Two patterns have been described. A ‘slow-flat-slow’ pattern is characterized by an initial slow phase in which delta waves appear and wave amplitude increases, a sudden flattening of the EEG, and a return to normal brain activity through a slow phase.
A ‘slow’ pattern consists only of an increasing and decreasing slowing. The slow-flat-slow pattern was considered to be a sign of more severe cerebral hypoperfusion and has been observed more commonly in cardio-inhibitory syncope compared with the other subtypes, and associated with the presence of convulsive movements during syncope. However, with the exception of small studies and the specific evaluation of convulsive-like movements during syncope, few studies have investigated both EEG patterns and signs and symptoms during syncope.

Van Dijk et al. (2014) describe signs and haemodynamic and EEG changes using videometric data in 69 cases of tilt-induced vasovagal syncope. Their results confirm that EEG flattening is a sign of more severe cerebral hypoperfusion than EEG slowing alone. Indeed, patients with the slow-flat-slow EEG pattern had a lower minimum blood pressure, longer ECG pauses and duration of loss of consciousness and more often had asystole than those patients with the slow EEG pattern. In addition, the authors analysed several clinical signs occurring during syncope, according to the EEG pattern of the patient and the phase in which they occurred. As already underlined in previous studies, pallor, sweating of the forehead, temporary cardiac asystole, and the absence of the P wave might help with the differential diagnosis of transient loss of consciousness.

In conclusion, from a clinical standpoint, this study can help us in recognizing syncope associated with a deeper hypoperfusion, which might be more symptomatic and require more diagnostic and therapeutic effort. Moreover, the description of symptoms that have rarely been described as associated with syncope, such as oral automatisms, might eventually help with the differential diagnosis of transient loss of consciousnesses with atypical clinical patterns.

Monica Solbiati1 and Robert Sheldon2

1Medicina ad Indirizzo Fisiopatologico, Dipartimento di Scienze Biomediche e Cliniche ‘L. Sacco’, Ospedale ‘L. Sacco’, Università degli Studi di Milano, Milano, Italy
2Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, AB, Canada

Correspondence to: Robert Sheldon, MD, PhD, FRCPC, Professor of Cardiac Sciences, Libin Cardiovascular Institute of Alberta of the University of Calgary, 3280 Hospital Drive NW, Calgary, AB, Canada, T2N4N1
E-mail: sheldon@ucalgary.ca

doi:10.1093/brain/awt363

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A (mini) pill for stroke?

In this issue of *Brain*, Bushra Wali *et al.* (2014) describe the efficacy of progesterone in an animal model of ischaemic stroke and, in so doing, provide data of importance for clinical translation, while at the same time raising the bar for high quality reporting of *in vivo* research (Wali *et al.*, 2014).

The development of new treatments for stroke is a tricky business (O’Collins *et al.*, 2006), and so finding an established drug that might have therapeutic efficacy is a tantalizing prospect. Abundant preclinical data support a neuroprotective effect of progesterone in experimental stroke and traumatic brain injury, and a phase III trial is under way. Given that the safety profile of progesterone is already known, such reprovisioning would accelerate drug development. A potential confounding influence is sex- and age-related differences in circulating progesterone. Women who experience stroke are usually post-menopausal, and modelling the menopause in animals is generally achieved by ovariectomy. In a meta-analysis of the effects of progesterone in animal models of focal cerebral ischaemia, Wong *et al.* (2013) found that progesterone increased mortality in young female hormonally-intact animals, and had no effect on lesion volume in adult ovariectomized females (Wong *et al.*, 2013). In human studies, patients taking hormone replacement therapy (either oestrone alone or oestrogen plus progesterone) at the time of their stroke seemed to have a worse outcome (Bath and Gray, 2005); however, the effect of progesterone on its own is unknown.

Wali *et al.* (2014) avoid the confounding effect of circulating progesterone and effects of ovariectomy by restricting attention to aged (12-month-old) male rats. They systematically explore the efficacy in ways that will help inform clinical trial design. For delay to treatment, the authors establish that efficacy is retained at 6-h delays but lost at 24-h delays, thus validating the use of a 6-h window in clinical trials. For drug dose, they show maximum efficacy at the lowest dose tested [16 mg/kg on Day 1 (in two doses 5–6 h apart), 8 mg/kg for the next 6 days], with 32 mg/kg (Day 1)/16 mg/kg thereafter marginally less effective, and 64 mg/kg (Day 1)/32 mg/kg thereafter clearly less effective. These doses are at the higher end of those identified in the review of Wong *et al.* (2013) who found no dose-response relationship. These dosage regimens are, however, loosely analogous to those that have been used in some clinical trials in traumatic brain injury, where the total daily dose has ranged from 2 mg/kg to 12 mg/kg.

The study by Wali *et al.* (2014) is also important in that it explores efficacy in aged animals with outcomes measured at extended times after the stroke has occurred. One difficulty in assessing the efficacy of drugs used to treat stroke is that residual infarct volume may be a poor guide to functional improvement, and in many animal models (Howells *et al.*, 2010) the neurobehavioural consequences of focal cerebral ischaemia resolve rapidly, meaning that long-term efficacy is difficult to measure. Using a combination of behavioural endpoints, Wali *et al.* (2014) demonstrate firstly that there is a sustained behavioural deficit 3 weeks after the injury, and secondly that the efficacy of progesterone was retained at these later time points. This response appeared to be independent of the delay to treatment—that is, the beneficial effect of treatment initiated 6 h after the induction of focal ischaemia was retained whether outcome was measured 3 days, 9 days or 21 days later. Conversely, the lack of benefit of treatment initiated 24 h after ischaemia was largely consistent across times of outcome measurement, although it is a simplification to say there was no efficacy with late treatment; for locomotion (distance travelled in the open field) and for measures of gait quality (stride length, paw print area, limb swing speed) the data are consistent with a biologically important effect, which the experiment was not powered to detect. As the authors point out, if efficacy is sustained beyond 6 h this would substantially broaden the pool of patients potentially eligible for progesterone treatment. This efficacy at longer delays to treatment suggests effects on regeneration and repair as well as neuroprotection, consistent with reports that progesterone promotes post-ischaemia synaptogenesis (Zhao *et al.*, 2011), increases circulating endothelial progenitor cells (Li *et al.*, 2012), and promotes neurogenesis (Barha *et al.*, 2011) and neural regeneration (Li *et al.*, 2012).

The most important thing about this study, however, is the effort made by the authors to minimize the risk that their findings are confounded by bias (Kilkenny *et al.*, 2010; Landis *et al.*, 2012). By randomly allocating animals to the various experimental groups, they ensure that the only systematic differences between the groups were those designed into the experiment. Of course, there will be differences between laboratory animals, but the investigators performed a power calculation to ensure that their experiment was large enough to account for these chance differences and still see any treatment effects of a size considered important. The authors take care to report the number of animals recruited to each experimental cohort, and the number surviving the experiment was large enough to account for these chance differences and still see any treatment effects of a size considered important. The authors take care to report the number of animals recruited to each experimental cohort, and the number surviving the experiment was large enough to account for these chance differences and still see any treatment effects of a size considered important. The authors take care to report the number of animals recruited to each experimental cohort, and the number surviving the experiment was large enough to account for these chance differences and still see any treatment effects of a size considered important.