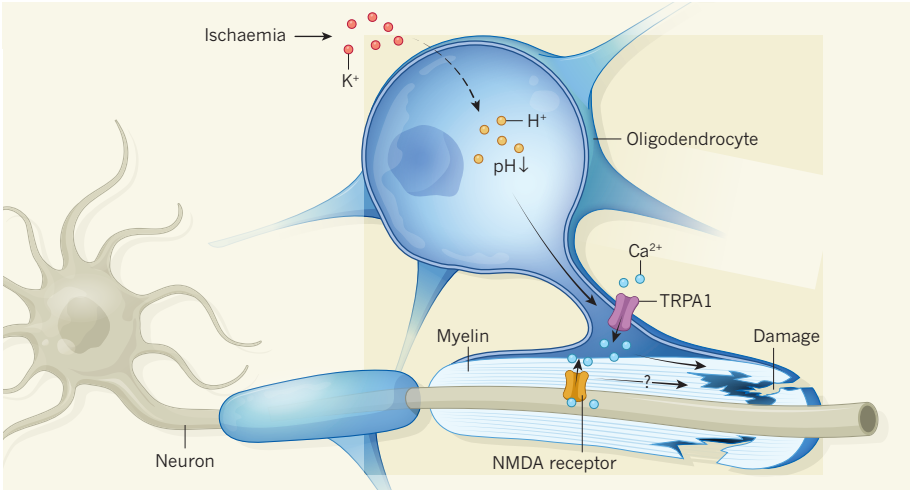


Figure 1 | Myelin injury in a model of ischaemia. Oligodendrocyte cells wrap around neurons and produce an insulating stack of membranes called myelin that speeds up neuronal signal transmission. When brain regions are deprived of glucose and oxygen (a condition called ischaemia), oligodendrocytes and myelin become damaged. Hamilton *et al.*[2] report that this damage is caused, in part, by a pathway that involves an increase in extracellular levels of potassium ions (K^+). Through an unknown mechanism (dashed arrow), increased K^+ levels trigger an intracellular rise in hydrogen ions (H^+). This reduces the pH in the cell, activating TRPA1-channel proteins and leading to an influx of calcium ions (Ca^{2+}). High levels of Ca^{2+} are toxic to oligodendrocytes and damage myelin. Glutamate-receptor proteins such as NMDA-type receptors can also mediate Ca^{2+} influx, but whether they have a role in ischaemia-evoked myelin damage in this setting is unclear.

from rats, the authors showed that blocking TRPA1 channels during oxygen and glucose deprivation reduced myelin damage, but had no effect on axonal injury. Thus, unlike the case with oligodendrocytes, damage to axons is mediated not by the activation of TRPA1 channels, but by other mechanisms of Ca^{2+} influx.

Hamilton *et al.* also detected spontaneous Ca^{2+}-level changes in the myelin of some normal oligodendrocytes, which were not deprived of glucose and oxygen. This spontaneous activity is probably indicative of axonal activity and the concurrent release of glutamate. So, given that myelin contains AMPA/kainate and NMDA receptors[5–7], and that ischaemia-evoked Ca^{2+}-level changes in optic nerves have previously been shown to be caused by activation of glutamate receptors[5], why did the authors not find evidence for glutamate-evoked Ca^{2+} changes?

The levels of the messenger RNAs that encode NMDA receptors are low in mature oligodendrocytes, but the levels of TRPA1 mRNA are almost undetectable[8], and the researchers still detected TRPA1-mediated Ca^{2+} influx in cerebellar oligodendrocytes. Evidence indicates that NMDA receptors move to myelin processes that face the axonal surface as oligodendrocytes mature[5,6]. This might help to explain why glutamate-evoked Ca^{2+} responses are difficult to detect in oligodendrocytes. Alternatively, perhaps oligodendrocytes in the optic nerve, which myelinate axons of only glutamate-releasing neurons, are different from the cerebellar oligodendrocytes that also myelinate neurons producing a different neurotransmitter, GABA.

In contrast to the current paper, a study published last month[9] provided evidence that, in optic nerves, NMDA and AMPA/kainate receptors do indeed act to mediate Ca^{2+} influx in mature myelin. Such influx in myelin is mediated by axonal activity and the vesicular release of glutamate. However, beyond the level of Ca^{2+} signals, the physiological functions of oligodendroglial NMDA receptors still need to be resolved.

Hamilton and colleagues' study demonstrates that *in vitro* damage to myelin owing to oxygen and glucose deprivation is more complex than anticipated, with TRPA1 channels joining the scene. Whether the results apply *in vivo* or to human TRPA1 channels, which have a different pharmacological response from those of mice[10], remains to be seen. Trials of NMDA-receptor blockers in people who have had a stroke have largely failed, in part because the drugs were administered too late, given the low doses at which their adverse side effects can be tolerated. Identifying other pharmacological targets raises the hope that safer drugs may be found. ■

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1. Nave, K.-A. *Nature* **468,** 244–252 (2010).
2. Hamilton, N. B., Kolodziejczyk, K., Kougioumtzidou, E. & Attwell, D. *Nature* **529,** 523–527 (2016).
3. Tekkok, S. B., Ye, Z. & Ransom, B. R. *J. Cereb. Blood Flow Metab.* **27,** 1540–1552 (2007).
4. Follett, P. L., Rosenberg, P. A., Volpe, J. J. & Jensen, F. E. *J. Neurosci.* **20,** 9235–9241 (2000).
5. Micu, I. *et al. Nature* **439,** 988–992 (2006).
6. Salter, M. G. & Fern, R. *Nature* **438,** 1167–1171 (2005).
7. Káradóttir, R., Cavelier, P., Bergersen, L. H. & Attwell, D. *Nature* **438,** 1162–1166 (2005).
8. Zhang, Y. *et al. J. Neurosci.* **34,** 11929–11947 (2014).
9. Micu, I. *et al. Exp. Neurol.* **276,** 41–50 (2015).
10. Nagatomo, K. & Kubo, Y. *Proc. Natl Acad. Sci. USA* **105,** 17373–17378 (2008).

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BIOANALYTICAL DEVICES

Technological leap for sweat sensing

Sweat analysis is an ideal method for continuously tracking a person's physiological state, but developing devices for this is difficult. A wearable sweat monitor that measures several biomarkers is a breakthrough. SEE LETTER P.509

JASON HEIKENFELD

Athletics trainers, physicians and even local pharmacists can take a sample of blood, saliva or urine and measure a whole panel of analytes (dissolved compounds) to reveal your physiological status at the time of sample collection. But none of the measurement techniques involved is conveniently portable or can continuously collect data for many hours or days — with the exception of glucose monitoring, which typically requires blood samples to be drawn by needle at regular intervals. On page 509 of this issue, Gao *et al.*[1] report a truly non-invasive, continuous biomonitoring device: a wearable, Bluetooth-enabled band containing a panel of sensors for sodium, potassium, lactate, glucose and skin temperature. And rather than using the body fluids mentioned above, the device measures analytes in human sweat.

Making a wearable band that electrochemically senses sweat analytes is extremely difficult. The sensors must be prepared from

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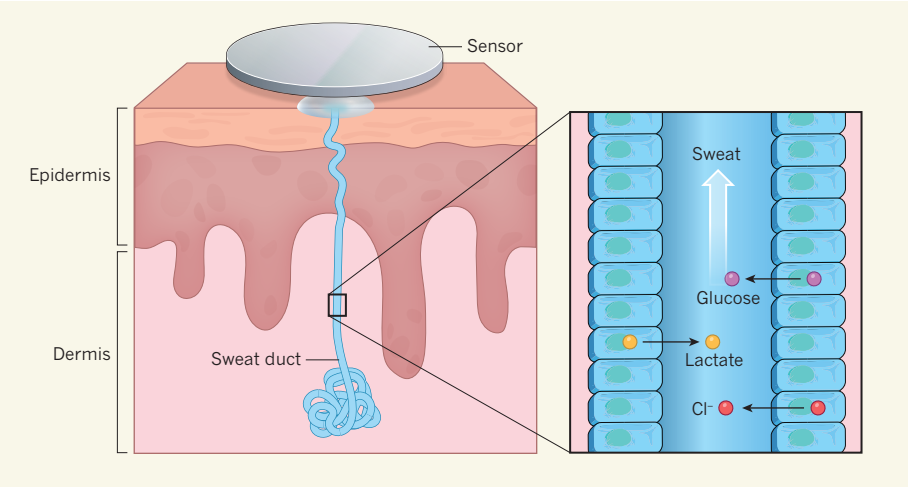


Figure 1 | Analysing sweat. Many biomarkers for a subject's physiological state, such as glucose, lactate or chloride ions (Cl^-), enter sweat from cells that form the walls of sweat ducts inside the skin. Gao *et al.*[1] report devices that can be worn as wrist or head bands, and which continuously analyse several molecules and ions in sweat using sensors placed on the skin's surface. (Adapted from ref. 2.)

scratch from basic chemicals — they can't just be purchased like the accelerometer chips used in smart watches and activity trackers. Another challenge is creating electronics that work with the ultra-high electrical impedance of the sensors. Basically, you need to figure out how to take a potentiostat — a device used to control electroanalytical experiments that typically weighs more than 2 kilograms — and make it so small and thin that you can wrap it around your wrist.

For decades, sweat analysis was relegated mainly to medical labs; this hampered its broader use for two reasons. The first is obvious: who can afford to tote around a cadre of trained medical staff and the associated equipment? The second reason is that conventional clinical methods for sweat collection and sensing could lead to inaccurate measurements. This is because existing clinical infrastructure is ill-equipped to work with the tiny volumes obtainable from sweat.

Gao *et al.* address these problems by putting tiny electronic sweat sensors right up against the skin (Fig. 1) — an approach that others have also reported[2–6]. Sweat and its analytes are thus quickly measured as they emerge onto the skin's surface. These sensors are highly electrochemically selective[3], and, despite their miniature sizes (on the order of square millimetres or smaller), they can distinguish a single type of ion or molecule from thousands of others in sweat.

This ability is a real leap forward for wearable devices, and couldn't have been made just by improving the rudimentary electrical or optical sensors found in commercially available activity trackers. For example, commercial trackers at best use a simple measure of electrical conductance on skin as a non-quantitative measure of sweat rate, whereas measuring sodium and potassium concentrations with electrochemical sensors quantifies sweat rate[2] and could also quantify the total amount of electrolytes lost during exercise.

Importantly, Gao and colleagues' devices use many sensors. Previous devices have been limited to a single sensor, which could generate misleading information — if a standalone sensor shows a signal change, it could be because sweating has stopped, because the sensor has fallen away from the skin, or even because the sensor is failing. Having multiple sensors can clarify what is happening. For example, potassium levels in sweat are fairly invariant with sweat rate and with normal physiological changes in the body[2]. So if there is a change in sodium, lactate or glucose signals while the potassium signal holds steady, then the other sensor changes can be trusted to be caused by a real physiological event.

The Bluetooth capability of their devices enabled Gao *et al.* to monitor continuously recorded data for at least an hour, and the types of sensors and electronics used should, in theory, enable such monitoring for 24 hours or more. Previously reported devices lacked Bluetooth. Having this capability is certainly commercially relevant, and start-up companies have developed functional, but unpublished, Bluetooth sweat-sensing technology in the form of watches[7] or patches[8].

The potential applications of wearable sweat-sensing devices extend well beyond those related to exercise. For example, the hormone cortisol is a marker of stress, and its concentrations in sweat are similar to those found in blood[2], making it a possible target for future monitoring. Even small-molecule drugs and their metabolites come out in sweat, so this body fluid might one day be used to monitor the amount of active drug in a patient's blood — helping to avoid rises and falls in drug levels between doses.

Today's commercially available wearables largely rely on decades-old technology. Their market success is due to a convergence of improved affordability and ergonomics and a rapidly growing consumer awareness of health. The next watershed in wearables will probably be driven by scientific breakthroughs. Sweat biomonitoring arguably has the greatest potential among the emergent non-invasive technologies. But such potential will go unfulfilled unless scientists dig into the unresolved 'hard science' of this approach.

For example, cutting-edge, commercial, point-of-care blood sampling and sensing technologies proudly claim that as little as 20 microlitres of blood are needed for some tests. But square-millimetre-sized sensors on the skin will receive, at most, several nanolitres of sweat per minute[2]. Just placing such sensors against the skin does not fully resolve this problem, because the gap between a sensor and the rough surface of the skin is so large that it takes periods of tens of minutes for fresh samples of sweat to displace previously accumulated sweat[2]. Although not exactly real-time monitoring for your workout, this a good start, and is certainly better than repeated blood draws.

Consider also possible applications involving situations in which you are unlikely to be sweating, such as monitoring your medication levels while at the office. Methods exist for locally stimulating sweat by iontophoresis — that is, using a tiny electrical current to drive a chemical sweat stimulant into the skin. But these methods were commercialized for collecting single sweat samples, not for repeated or prolonged sweat monitoring throughout a day or week. Alternative methods must therefore be developed.

Fortunately, the remaining challenges for sweat biomonitoring do not seem to be fundamental impediments. As Gao and colleagues' work, and that of others[2–6], reveals the scale of the opportunities in this field, researchers will undoubtedly come up with innovations to transform technology that is currently merely appealing into something that, one day, you could not imagine living without. ■

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1. Gao, W. *et al. Nature* **529,** 509–514 (2016).
2. Sonner, Z. *et al. Biomicrofluidics* **9,** 031301 (2015).
3. Bandodkar, A. J. & Wang, J. *Trends Biotechnol.* **32,** 363–371 (2014).
4. Huang, X. *et al. Small* **10,** 3083–3090 (2014).
5. Rose D. P. *et al. IEEE Trans. Biomed. Eng.* **62,** 1457–1465 (2015).
6. Matzeu, G. *et al. Anal. Meth.* **8,** 64–71 (2016).
7. www.idtechex.com/research/articles/idtechex-printed-electronics-usa-2014-award-winners-00007085.asp
8. www.eccrinesystems.com/sweatronicsplatform

The author declares competing financial interests: see go.nature.com/cvwyed for details.

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