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Neuroscience

A signal to synchronize thought with metabolism

Manfred Hallschmid & Jan Born

In a brain structure called the hippocampus, sharp wave-ripples — oscillatory hallmarks of an 'offline' mode of cognitive processing — have been found to predict dips in glucose concentrations in the body. **See p.82**

To regulate adaptive behaviour, the brain relies on a continuous flow of cognitive and memory-related processes that require a constant energy supply. Weighing around 1,200 grams in women and 1,300 grams in men, on average, the brain consumes around 90 grams, or 340 kilocalories' worth, of glucose per day, accounting for around half of the body's glucose demand[1,2]. The tight integration of metabolic and cognition-related signals might aid the matching of the brain's energy supply to its energy needs, by optimizing foraging behaviour and efforts to limit energy expenditure. The synchronization of glucose supply with brain activity has so far been considered a function of a structure called the hypothalamus, at the base of the brain. On page 82, Tingley *et al.*[3] provide evidence in rats for the role of another brain region, called the hippocampus, which is typically implicated in memory and navigation, in this equation (Fig. 1).

The hippocampus receives many types of sensory and metabolic information, and projections from neuronal cells in the hippocampus extend to various parts of the brain, including the hypothalamus. Thus, the hippocampus might indeed represent a hub in which metabolic signals are integrated with cognitive processes[3]. To examine this possibility, Tingley and colleagues recorded oscillatory patterns called sharp wave-ripples (SPW-Rs), reflecting changes in electrical potential across the cell membranes of neuronal-cell ensembles in the hippocampi of rats. They did this while using a sensor inserted under the skin of the animals' backs to continuously measure glucose levels in the interstitial fluid surrounding the cells there.

SPW-Rs are composed of a sharp wave, arising from neurons in the CA3 region of the hippocampus, that brings about a fast but localized network oscillation — the ripple — in the CA1 and connected regions. Crucially, SPW-Rs are associated with synchronous bursts of neuronal firing, and represent a hallmark of cognitive, specifically memory-related, processing of experience[4].

The authors demonstrated that clustered SPW-Rs recorded in a part of the hippocampus called the dorsal CA1 are followed by a distinct drop in peripheral glucose concentrations around 10 minutes later. Although the rate of SPW-Rs, which averaged almost 10 per minute, varied considerably over a 24-hour cycle, the authors show that a reduction in glucose concentrations of about 0.33 milligrams per decilitre emerged per SPW-R. SPW-Rs that had a large amplitude but short duration and were clustered together in time predicted the most-pronounced drops in glucose.

This striking observation suggests a previously unknown role of SPW-Rs as a phase-resetting signal to control an animal's glucose levels. Certain aspects of this proposed role require some thought, including the timing of the observed glucose responses. The delay of roughly 10 minutes between SPW-Rs and the drop in glucose might be explained by factors such as the low speed of the diffusion of glucose into the interstitial space, and a technical delay that is inherent in an implanted sensor's glucose readout. Therefore, the coupling of the hippocampus and peripheral glucose levels through SPW-Rs might be even tighter.

Another aspect to be considered is the direction of change in glucose levels after SPW-Rs. These oscillatory patterns are associated with increased firing activity in the hippocampus,

From the archive

A look back at the life of Lawrence Bragg, and a call for London to erect a statue of Louis Pasteur.

50 years ago

Sir Lawrence Bragg, who died on July 1 aged 81, had the unique distinction of having himself created the science to which he devoted his life's work, and lived long enough to experience its revolutionary impact, first on inorganic chemistry and mineralogy, then on metallurgy, and finally on organic chemistry and biochemistry … Röntgen discovered X-rays when Bragg was five years old, and von Laue, Friedrich and Knipping demonstrated X-ray diffraction by crystals in the spring of 1912, when Bragg was taking his physics degree at Cambridge … By a remarkable feat of imaginative insight Bragg … reformulated von Laue's conditions for diffraction into what became known as Bragg's Law, which gives a direct relationship between the crystal structure and its diffraction pattern … If we think of Bragg as an artist and compare him to, say, Giotto, it is as though he had himself invented three dimensional representation, and then lived through all the styles of European painting from the Renaissance to the present day, to be finally confronted by computer art … To the present young generation Bragg was an avuncular figure who showed them that science can be fun. At the Royal Institution he instituted a series of physics lectures for sixth formers … Bragg's superb powers of combining simplicity with rigour, his enthusiasm, liveliness and charm of manner, and his beautiful demonstrations all conspired to make him one of the best lecturers on science that ever lived. **M. F. Perutz**

From *Nature* 3 September 1971

100 years ago

France is already preparing to celebrate … the centenary of the birth of Pasteur … If every Englishman and Englishwoman who has cause to be grateful to him and his followers would subscribe sixpence, we should obtain enough money for a lifesize golden image … It is one of our national disgraces that there is no memorial to him in London.

From *Nature* 1 September 1921

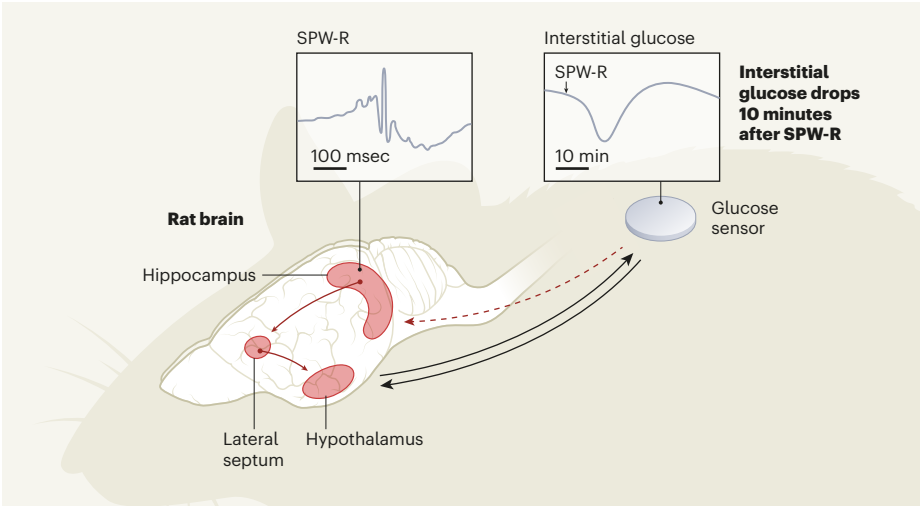

Figure 1 | Brain signals that regulate glucose levels in the body periphery. The hypothalamus in the brain helps to regulate glucose concentrations in the blood and in the interstitial fluid that surrounds cells in the body. This hypothalamic (feedback-mediated) regulation is activated, for example, during stress. Tingley *et al.*[3] provide evidence in rats that another brain structure, the hippocampus, also regulates peripheral glucose concentrations. In the hippocampus, oscillatory patterns — called sharp wave-ripples (SPW-Rs) — emerge in the collective electrical potential across the membranes of neurons. They seem to signal, by way of a region called the lateral septum, to the hypothalamus to produce dips in interstitial glucose concentration about 10 minutes later. The feedback mechanism in this regulatory loop is unknown (dashed arrow). Given that hippocampal SPW-Rs are a hallmark of the reprocessing of previous experiences, they might thus control the brain's energy supply during a 'thought-like' mode.

as well as in various parts of the brain's cortex that receive the hippocampal outputs. Therefore, given this increase in firing and, thus, possibly enhanced brain-energy demands, one might expect that the hippocampal signal leads to increased, rather than decreased, provision of glucose. In stressful situations, the brain can rapidly signal — through neurons of the sympathetic nervous system — to the rest of the body to increase peripheral glucose concentrations. However, during SPW-Rs, the brain regions that mediate sympathetic activation seem to be deactivated[5]. Could it be, then, that the glucose reductions after SPW-Rs simply reflect the brain's increased consumption and the 'pull' of peripheral glucose to the brain during SPW-Rs?

Clever control experiments performed by Tingley and colleagues suggest that this is not the case. They found that artificially inhibiting the lateral septum, a major relay station for the signal from the hippocampus to the hypothalamus, abolished the coupling of SPW-Rs with peripheral glucose fluctuations. This finding, and the observation that artificially induced hippocampal ripples were likewise followed by glucose dips, corroborate the idea that a signal specifically associated with SPW-Rs, and that is transmitted by way of the hypothalamus, induces drops in glucose availability in the body periphery.

These results might spawn fresh ideas about how the regulation of glucose supply to the brain is integrated with the homeostatic regulation of glucose turnover in the whole animal. Moreover, because the SPW-R–glucose coupling was the same when the animals were fasted as when they could eat freely, these findings cast new light on the assumption that systems in the brain control blood-glucose levels under normal conditions[6], and not just in the face of stress and other metabolic challenges. Future studies should investigate whether the SPW-R-associated drops in glucose occur throughout the whole animal or reflect a redistribution of energy that prioritizes the brain[7], and should identify the underlying mechanisms.

SPW-Rs are not mere companions of strong increases in neuronal firing activity: during these patterns, the hippocampus replays, in a time-ordered manner, experiences that have previously been encoded into memory. SPW-Rs do not occur when a rat is actively exploring a maze. Instead, they occur during short rests between periods of locomotion, when the rat seems to 'plan' where to go next. They also occur during episodes of slow-wave sleep (sleep characterized by low-frequency electrical oscillations) after exploratory behaviour, when lasting memories of the experience are to be laid down. During SPW-R replay, pre-existing traces of information might be combined to influence decisions[4]. Thus, it seems that SPW-Rs characterize an 'offline' mode during which the hippocampus and connected brain areas engage in 'thought-like' activity.

In this light, the findings by Tingley *et al.* link discrete periods of thought-like reprocessing of previous experiences to immediate metabolic regulation. Given that SPW-Rs also coordinate hippocampal activity with the activity of ensembles of neurons in cortical output areas of the hippocampus, they might even serve to enable widespread parts of the brain to exert cognitive control over peripheral metabolism while in offline mode. Recent findings suggest that thought-like memory-related activity, as reflected by SPW-Rs and that typically emerges in moments devoid of acute stress, might profit from synchronized, small shortfalls in energy supply[8]. Indeed, this might be a first hint of an explanation as to why hippocampal SPW-Rs should downregulate, rather than upregulate, peripheral glucose concentrations.

In summary, the intriguing results by Tingley and colleagues point to the existence of a hitherto unknown hippocampal loop that underlies cognitive control of the regulation of blood glucose. The authors' findings not only open up fresh perspectives for basic research, but also prompt reconsideration of various clinical phenomena. These include the co-occurrence of cognitive decline and, notably, hippocampal deterioration with impaired glucose regulation in type 2 diabetes[9]; the association of disturbances of slow-wave sleep with insulin resistance[10]; and the dysregulation of food intake in individuals who have hippocampal lesions and associated memory impairments[11]. It is tempting to speculate that the loss of metabolic control in these conditions might have a common cause in the dysfunctional expression of hippocampal SPW-Rs.

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