EDITORIAL

The Energetic Cost of a Night on the Town

Commentary on Plante et al. Gray matter-specific changes in brain bioenergetics after acute sleep deprivation: a ^{31}P magnetic resonance spectroscopy study at 4 Tesla. SLEEP 2014;37:1919-1927.

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In this issue, Plante and colleagues[1] look at the effect of a night of sleep deprivation on brain bioenergetics measured by ^{31}P magnetic resonance spectroscopy (MRS) in eight healthy young individuals. Interestingly, the study includes investigation of bioenergetic changes after the subsequent two nights of restorative sleep, and it reveals that the impact of a night's lost sleep takes some time for the brain to resolve.

The study confirms that a night without sleep is, in the short term, without significant penalties in high energy phosphates (i.e., ATP and phosphocreatine)[2,3] and reinforces the findings of an earlier study from these authors' laboratory that bioenergetics are altered after one night of restorative sleep. The bioenergetic changes are also stratified by whether they occur in gray or white matter areas of the brain, with different biochemical consequences depending on the tissue type. This work adds to the growing and increasingly detailed literature showing that sleep is important for restorative and anabolic processes and that these processes are likely cumulative without sleep.

Of course, this study raises many more questions and issues than can be addressed in a small study of only eight people.

It is known that there are significant cognitive decrements caused by lack of sleep, particularly those that require rapid processing,[4] a skill that is related to mitochondrial phosphorylation potential,[5] a marker of which is the relationship of inorganic phosphate with ATP levels (Pi/ATP). It is also known that brain glucose use declines significantly with lack of sleep,[6] but paradoxically there is increased whole body energy expenditure.[7] The fact that brain bioenergetics maintain equilibrium after a night of lost sleep is all the more remarkable, as plainly, like the swan moving effortlessly across a river, a lot of activity is going on underneath.

In the first hours of normal sleep in rats, ATP levels "surge." This is speculated not to be "restorative" but to deal with the energy requirements of anabolic processes that take place during sleep.[8] It would be useful to know if this surge also happens in humans and also whether ATP levels measured at the approximately 3 am nadir of the circadian core temperature cycle would remain unchanged with sleep deprivation. Timing may be important; a ^{1}H MRS study that measured occipital lobe biochemistry at 11 pm the day following a night of sleep deprivation showed decreased *N*-acetylaspartate (a mitochondrial and neuronal marker) and decreased total choline in eight healthy women, consistent with impaired energy metabolism.[9]

It is also not possible to infer from the report by Plante et al.,[1] the extent to which heterogeneity in the response to sleep deprivation[10] influenced the results. The early ^{31}P study of sleep deprivation by Murashita et al.[2] suggested that there might be differences in baseline brain pH between those who experienced decline in high energy phosphates compared to those that did not. This is in keeping with the evidence that baseline brain activity,[11] perfusion,[12] or connectivity[13] may predict neurobehavioral vulnerability to sleep loss.

Also curious are the findings in white matter of changes in pH and Pi following restoration sleep. Putting aside that very few voxels in the brain contain purely white matter, little is known about the relationship between brain ^{31}P measures in white matter as the majority of white matter measurements have been static rather than dynamic. The lack of change in ATP or phosphocreatine seems to indicate that the reported white matter changes are outside the usual creatine kinase sphere,[14] but it is not immediately apparent how they fit into the biochemical system. Little is also known about oligodendrocyte metabolism or the bioenergetic costs of myelin maintenance, although Plante et al.[1] point to the recent finding that glycolytic oligodendrocytes[15] are involved in regulation of ATP and pH during myelin maintenance,[16] which may take place via the silent information regulator SIRT2.[17] Furthermore, given that baseline levels had still not been attained after two nights' recovery sleep, how long does it take to recover fully?

This work raises another issue; how do we best deal with this sort of systems biology data? ^{31}P Magnetic resonance spectroscopy is one of the few methods we can use to measure brain bioenergetics noninvasively. High energy phosphates ATP and phosphocreatine are exquisitely responsive to brain activity, changing and measurable on a seconds time scale, along with brain pH, inorganic phosphate and alterations in brain phospho-mono- and phosphodiesters. One major drawback of MRS is its general insensitivity. Because of this, spectra must be sampled from a relatively large area of brain. As a consequence, the spectrum captures the net sum of activity in all brain compartments within the relatively large area that must be sampled in order to obtain adequate signal to noise.

How, then, do we interpret the underlying cause of any changes in the spectrum when we do not know about the myriad of things that might be happening in all the individual compartments of ATP or pH or creatine kinase activity? Firstly, it is essential to use all metabolites from the spectrum to make as much use of the biochemical snapshot as possible. Plainly,

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the key molecules are highly interlinked so that we should treat them as a system, rather than as discrete entities.

The data of Plante et al.[1] would benefit from the multivariate analyses used for example in the metabolomics communities, and which are now beginning to be used in analysis of magnetic resonance spectra in vivo.[18] These latter approaches use the data from the entire system rather than the limited sample obtained by considering all variables singly and independently. This is important when considering what has happened in a system in which an elevation in ATP could mean something entirely different depending upon what other changes may have accompanied it.

Sleep deprivation studies are expensive and time consuming, so it is essential in these and in other similar investigations to wring the most out of the data and analyze them using an optimal statistical strategy. Not only would this make it easier to make sense of the outcomes but also give us a more robust framework to assess the reliability of data. Nevertheless, there is plenty of food for thought in the report by Plante and colleagues.[1]

CITATION

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DISCLOSURE STATEMENT

Dr. Rae has indicated no financial conflicts of interest.

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