What is the Meaning of the ATP Surge During Sleep?


Margaret Wong-Riley, PhD
Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, WI

The recent paper by Dworak et al.1 reported a surprising finding, that there was a “surge in ATP levels” in the initial hours of spontaneous sleep in several brain regions, that the “surge” was prevented or delayed by sleep deprivation, and that an inverse relationship existed in diurnal fluctuations between ATP and P-AMPK levels. The authors hypothesized that “sleep is for an energy surge” permitting “energy-consuming anabolic processes, such as protein and fatty acid synthesis, to occur.”

The necessity for sleep is universally accepted. Sleep deprivation, especially when prolonged, can lead to multi-system dysfunctions, even death.2 The lingering question has been, “What feature(s) of sleep is(are) necessary for health and for life?” Benington and Heller’s3 proposal that sleep is for the restoration of brain energy metabolism is attractive, and their focus was on astrocytic glycogen store for the replenishment of energy. Dworak et al. challenged the concept of restoration and proposed that the sleep-induced ATP “surge” is the key for anabolic processes.

The first question that comes to mind with the spike in ATP level is, “Does this reflect an increase in ATP synthesis, a decrease in ATP degradation, and/or a decrease in ATP usage?” This is central to the argument of a “purpose,” if there is one, for such a “surge.” If the surge is dependent on ATP synthesis and is necessary for anabolic functions, then one has to ask, “Is there a difference in protein synthesis between awake and asleep?” and “Does anabolic activity require ATP levels that far outweigh the ATP needs of other functions?” To the first question, the extensive study on 57 brain regions of monkeys showed no statistically significant difference in protein synthesis rates between awake and asleep states (although a significantly higher rate was found during deep sleep versus light sleep).3 In the rat suprachiasmatic nucleus with an endogenous circadian pacemaker, no evidence in circadian rhythm of protein synthesis was detected.4 The screening of 10,000 genes in rats revealed that most genes were up-regulated in wakefulness and sleep deprivation as compared to sleep, and not vice versa.5 However, even if protein synthesis rates were higher during sleep than wakefulness, it leads naturally to the second question posed above. The answer, based on the published data thus far, supports the conclusion that protein synthesis consumes relatively little energy.5,6 In the rabbit retina or the rat brain, protein synthesis accounts for only 1.3-2% of total energy consumption,8,9 and phospholipid turnover consumes only ~5%.9 By all accounts, the bulk of energy consumed by neurons is for the active transport of ions against their concentration and electrical gradients in relationship to neuronal activity, i.e., the more frequently a neuron’s membranes are depolarized by excitatory input, the greater its energy demand for repolarization.9,10 Much of this energy is consumed by dendrites, the major receptive sites for excitatory synapses.10

If anabolic activities are not likely to be the major reason for increased ATP synthesis (and this can be further tested with protein synthesis inhibitors), then what, if any, function(s) during sleep would require such a surge? In rats, both NREM and REM occur in both the light and dark cycles, and bouts of wakefulness exist in the light cycle.11 If the surge of ATP is related to NREM activity, as Dworak et al. suggested, then shouldn’t there be a similar “surge” around the 7th-8th hour of the dark cycle, when there is much NREM activity (see Figures 1 and 7)? If brain metabolic activities during wakefulness and REM are greater than those during NREM,12,13 then the relatively low ATP levels (compared to the “surge”) should reflect greater ATP usage during the waking period that consumes the energy generated. In neurons, energy is not generated unless energy is used.14 So, the ATP “surge” is not likely to be increased ATP synthesis, as the need and usage are reduced during this time. That leaves a decrease in ATP degradation with an accumulation of unused ATP as another plausible explanation for the “surge.” This is consistent with authors’ findings of a delay or prevention of “surge” when the animals were sleep-deprived, i.e., when their energy consumption was increased. A high level of ATP is inhibitory to cytochrome c oxidase,15 a terminal enzyme of the mitochondrial electron transport chain. Such inhibition limits further energy generation, with a possible benefit of preventing excessive accumulation of reactive oxygen species, a byproduct of energy metabolism.

Dworak et al.’s findings are indeed intriguing and provocative. However, the rationale for the ATP “surge,” at least for this reader, deserves further probing.

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REFERENCES


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Address correspondence to: Margaret Wong-Riley, PhD, Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226; Tel: (414) 955-8467; Fax: (414) 955-6517; E-mail: mwr@mcw.edu

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