Intracellular magnesium and the rhythms of life

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Circadian (about daily) rhythms are driven by cell-autonomous biological clock mechanisms that allow organisms to anticipate and adapt to the environmental cycle of day and night.

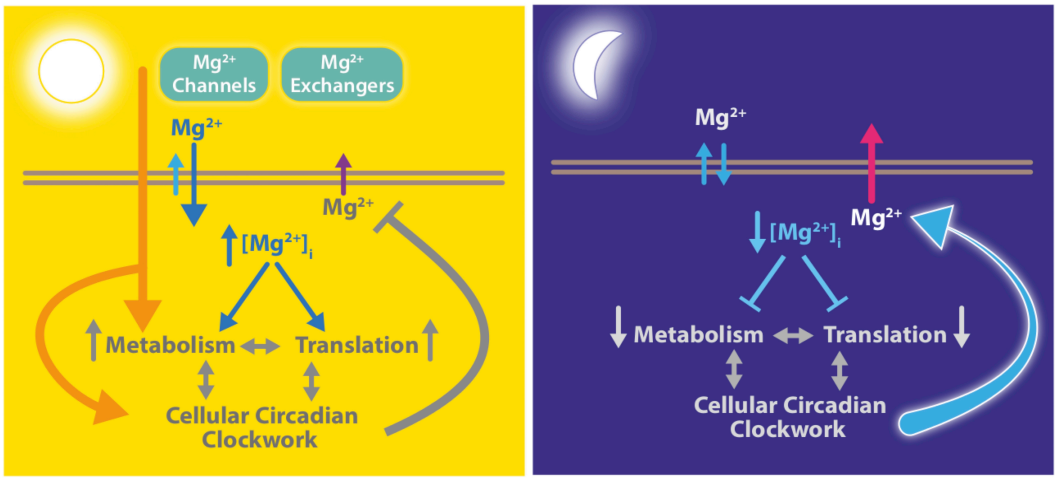
In a recent publication in Nature[1], we revealed novel circadian rhythms in the concentration of intracellular magnesium, $[Mg^{2+}]_i$, in a range of eukaryotic cells: a human cell line, mouse fibroblasts, a marine unicellular alga, and a filamentous fungus. Treatments affecting $[Mg^{2+}]_i$ influenced key clock parameters in human as well as algal cells, indicating that magnesium rhythms are crucial to cellular circadian timekeeping. Given the role of magnesium ions as NTP cofactors, $[Mg^{2+}]_i$ rhythms provide an astonishingly effective means to dynamically tune cellular biochemistry, and time energy consumption throughout the daily cycle to anticipate the differing metabolic demands placed upon cell physiology dictated by the Earth's rotation. Our findings indicate that circadian rhythms in $[Mg^{2+}]_i$ and their functional consequences evolved over a billion years ago and are pervasive across eukaryotic life. A brief reappraisal of previous links between magnesium ions and biological rhythms is therefore warranted.

Older observations have reported circadian $[Mg^{2+}]_i$ rhythms in whole organisms, and our findings therefore provide a cellular basis for understanding this earlier work. For example, as early as 1978, Kondo *et al*. showed that magnesium and potassium ions disappear from media in which duckweed is grown with a ~24-hour rhythm[2]. Uptake rhythms were not observed for calcium, closely mirroring our recent observation of intracellular oscillations in magnesium, potassium but not calcium in representatives of three eukaryotic kingdoms[1]. Similar to intracellular ionic oscillations, uptake rhythms were temperature compensated and entrained by light/dark cycles[3]. It seems reasonable therefore to assume that whole-organism uptake rhythms reflect the summation of individual cellular oscillations. Moreover, indications of circadian rhythms of magnesium content in mammalian organs also exist (e.g. [4]). Although highly suggestive of intracellular rhythms, the functional consequences of magnesium oscillations in tissues or whole organisms remain to be explored. However, our experiments certainly suggest that at the cellular level, $[Mg^{2+}]_i$ rhythms confer the capacity to dynamically tune ATP consumption and primary metabolism to the appropriate time of the day without impacting upon the absolute size of the ATP pool itself.

If approximately 24-hour rhythms in magnesium availability can tune metabolism over the daily cycle, then logically $[Mg^{2+}]_i$ regulation could tune metabolism to accommodate biological cycles of other durations and functions. Indeed, rhythms in intracellular magnesium were observed over the yeast cell cycle in the 80s, leading to theories that differential magnesium levels regulate cell cycle progression. As reviewed by Walker *et al*.[5], high intracellular magnesium was associated with the energetically costly processes of genome duplication, whilst at phases of low intracellular magnesium, only cell growth occurred. If this argument is further extended, dynamic regulation of $[Mg^{2+}]_i$ might also contribute to biological rhythms over even longer time scales, e.g. circannual rhythms. As early as 1938, the magnesium (but not calcium) content of serum from hibernating hedgehogs was observed to increase to 170% of the levels observed before onset of hibernation[6], with similar increases in serum magnesium levels reported for animals undergoing torpor. This increase can

obviously not be explained by nutrition, and therefore most likely reflects a decrease of intracellular magnesium. A plausible hypothesis that now needs to be tested with modern analytical techniques is that cells and tissues in animals progressing into torpor or hibernation actively deplete cellular magnesium in order to lower metabolic rates and minimise energy consumption. In fact, magnesium depletion could conceivably account for the mechanism by which these extremely low metabolic states are sustained. Questions arising from this line of reasoning would include whether magnesium levels are altered in dormant bacteria, bacterial and fungal spores, as well as dormant parasites in animal hosts. Furthermore, intracellular magnesium depletion could plausibly contribute to the dormant state of plant seeds, as well as neurons during animal sleep[7].

We are now at the point where the role of $[Mg^{2+}]_i$ in the dynamic regulation of cellular metabolism needs to be understood and translated into how co-ordination of tissue and organismal function is effected. Given the essential function of magnesium in our bodies, with the activities of an estimated 600 enzymes being Mg^{2+}-dependent, it is surprising how little is known about magnesium transport, compared with Ca^{2+}, for example. We urgently need to identify which molecular mechanisms underlie $[Mg^{2+}]_i$ oscillations and allow it to potentially serve as a 'meta-regulator' of metabolic state. Notably, magnesium oscillations regulated global translation rates (see Figure) at least partly due to the unusually high magnesium sensitivity of mTOR[1]. It is enticing to speculate on future applications for safer shift work or more comfortable intercontinental travel, but essential to remain cautious and realistic, as our knowledge is very much incomplete even at the cellular level. What is most apparent however, is that a full understanding of the dynamic regulation of metabolism via magnesium across different eukaryotes and timescales would unveil a huge number of potential applications throughout major areas of contemporary challenges to human societies, such as human metabolic health, food crop yields, and the productivity of microbial biotechnology.



Circadian regulation of $[Mg^{2+}]_i$ and feedback to the clockwork.
Circadian $[Mg^{2+}]_i$ oscillations are generated by dynamic membrane transport, tuned by the cellular clock. $[Mg^{2+}]_i$ rhythms have direct consequences for cellular energy consumption and metabolic rates. Rhythmic sunlight, $[Mg^{2+}]_i$ and metabolism all directly feed back to entrain the clock. Similar models can be drawn for biological rhythms of other period lengths (Figure created by LMB Visual Aids).

References:

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