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CIRCADIAN RHYTHMS

SCN synchronicity…hup, two, three, four

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It would be most inconvenient if your stomach thought it was time for breakfast while your eyelids thought it was bedtime. Luckily, neurons of the suprachiasmatic nucleus (SCN), which control the internal circadian rhythm, spontaneously synchronize so that their target neurons in peripheral tissues receive correctly time-coordinated signals. But how do the SCN neurons stay in sync? The results of new work reveal that interneuronal signalling via vasoactive intestinal polypeptide (VIP) is required.

Maywood and colleagues focused on VIP signalling, as it had previously been implicated in SCN circadian rhythmicity. To further investigate this association, the team looked at expression of the clock gene period (*Per*) in mice that lacked VIP receptor 2 (VIPR2). In normal mice, *Per* expression is temporally controlled by a feedback mechanism that results in a 24-hour periodicity between expression peaks. The group used a *Per1* transgene containing a bio-luminescent reporter and, in real time, measured the amount of light emitted from SCN slices in culture over a number of days. Compared with wild-type mice carrying the transgene, *Vipr2*$^{-/-}$ mice showed low levels of bio-luminescence and an imprecise periodicity. Furthermore, using video microscopy to continuously image the slices, the researchers were able to determine that rather than the regularity of feedback loop mechanism having been lost from all cells, the cells had instead lost synchronicity. Therefore, loss of VIP signalling both reduced the expression levels of *Per* and disrupted interneuronal synchronicity.

Expression of *Per* can be suppressed by hyperpolarization of SCN neurons. Therefore, to determine whether membrane depolarization might rescue the expression level of *Per* (and synchronicity) in *Vipr2*$^{-/-}$ mice, the team depolarized the SCN slices and found that both *Per* expression levels and interneuronal synchronicity of the feedback loops did revert to that of the wild type. The same result was observed when gastrin-releasing peptide (GRP), which activates electrical firing of SCN neurons, was added to the slices. However, once depolarization or GRP treatment ceased, the cells of the SCN gradually (over a period of days) lost synchronicity and *Per* expression levels dropped.

Taken together, the findings of Maywood *et al.* indicate that synchronicity of SCN neurons cannot be achieved by one initial signal but instead requires continued signalling (through VIP). Much like marching soldiers sing together to keep in sync, SCN neurons continually signal to each other to maintain sychronicity of the body clock.

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ORIGINAL RESEARCH PAPER Maywood, E. S. *et al.* Synchronization and maintenance of timekeeping in suprachiasmatic circadian clock cells by neuropeptidergic signaling. *Curr. Biol.* 21 March 2006 (doi:10.1016/j.cub.2006.02.023)