EDITORIAL

To slow down, or not to slow down (the intrinsic clock), that is the question!

In the beginning, 3.5 to 3.9 billion years ago, the length of day was about 14 hours and ultraviolet radiation was not filtered by the Earth's atmosphere. Thus, circadian clocks met the night-day transitions with the approximate period of 14 hours and were readily involved in protection from ultraviolet radiation. Thereafter, the period has lengthened, along with circadian clocks that have evolved a slowing-down mechanism (1, 2) and adopted periods of longer than 14 hours up to the current one of about 24 hours as the reference. Physiological functions and behaviours demonstrate daily and seasonal variations that are generated by the circadian clock (3).

Circadian clocks are endogenous pacemakers that evolve their properties, when subjected to selection, but have remained conservative during evolution (4). Genes that encode proteins for repression of transcription as "the breaks" are essential to the normal functions of circadian clocks (5). In humans, as well as in other mammals, cryptochrome circadian clock 2 (CRY2) and cryptochrome circadian clock 1 (CRY1) are the key repressors (6, 7). Of them, CRY1 is needed as a slowing-down mechanism (8). However, CRY2 has a key role in balancing the functions of the cryptochromes, as CRY2 opposes the actions of CRY1 and inhibits CRY1 from accessing its DNA targets too early (9).

In nature, exposure to environmental light and ambient temperature of the terrestrial 24-hour cycle act together to dictate the phase and synchronization of the circadian clock (10). Since most biochemical reactions respond robustly to temperature, it may be the original and universal time-giver to an organism (11). Evolution of the slowing-down and other mechanisms to anticipate and buffer the effects of day-to-day and season-to-season changes in ambient temperature is expected as beneficial and to favour adaptation (12, 13).

The change of seasons challenges the functions of the circadian clock (14), the change of winter to spring, when days are warm but nights are still cold, is an especially stressful period for the organism. Brown adipose tissue (BAT), whose activation follows a shorter (i.e. ultradian) period, guides the circadian rhythm of core body temperature that is the anchorage for all the remaining circadian rhythms in the body (15). Further, there is the efferent sympathetic and afferent sensory brain-BAT-brain neural feedback circuit for the control of functions of BAT (16).

Concerning diurnal animals, transcription of the cryptochrome genes is induced in the evening (17), and the heat-induced phase shifts of the circadian clock are severely reduced in the cryptochrome loss-of-function mutants (18). Hence, the cryptochrome proteins regulate the ability to synchronize by stemming from stimuli of temperature (19). If this were to hold for mammals, then as I hypothesize herein, dysfunction of CRY2, or perhaps that of CHRONO (20) which integrates behavioural stress and epigenetic control for the body, may allow the activation of BAT to affect the brain more easily. Heat generated by activated BAT might therefore disrupt the slowing-down mechanism of the circadian clock, and subsequently permit the ultradian oscillator of the mesolimbic dopaminergic cells to dominate and cause changes in mood and behaviour (21).

By this mechanism, the dysfunction of cryptochromes might account for both the circadian misalignment and the seasonal mismatch, and contribute to the pathogenesis of mood disorders and deaths from suicide. Now, the next step will be experimental studies to demonstrate whether or not BAT is active or activated abnormally in the depressed, and if it were, whether it contributes to their mood and mood-related behaviours.

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