EDITORIAL

Spring in psychiatry

A ray of light is seen again after the long winter. Spring induces two waves of transcriptional and translational activity in the brain. Under experimental conditions, the first wave is initiated about 14 hours after dawn of the first long day and includes transcription of the "long-day gene" *TSHB* (1-3). On May 2nd 2014, a publication elucidated a key mechanism that is relevant to mood and mood disorders (4). This molecular mechanism now links *TSHB* to the circadian clock protein NR1D1.

Earlier, NR1D1 has been linked to the core of the circadian clock (5) upon change from short to longer photoperiods (6), and on May 8th 2014, to the midbrain dopamine production and mood regulation (7). Due to these two publications released in May 2014, NR1D1 is, out of the blue, a hot spot in psychiatry, because, as already known, it is also a key for lithium treatment by its action on the circadian clock (8). Actions of lithium take place inside a neuron on a pathway where three circadian clock components (9) regulate mood through the activity of monoamine oxidase A (10) and contribute to the seasonal pattern for mood disorders (11-12). In addition to this indirect link, there is a direct interaction of circadian clock proteins with NR1D1 and other nuclear receptors (13).

Here, a key is the two cryptochromes which are circadian clock proteins. The cryptochromes oppose glucocorticoid receptor activation, and the deficiency of cryptochromes doubles the number of dexamethasone-induced genes in primary fibroblasts from the double-knockout mice (14). These double-knockout mice display constitutively high levels of circulating corticosterone, suggesting that there is a reduced suppression of the hypothalamic-pituitary-adrenal axis and that glucocorticoid transactivation in the liver is enhanced (14).

In addition to actions in the nucleus of a cell, the cryptochromes act as inhibitors of adenylyl cyclase and thereby limit cyclic adenosine monophosphate production (15). The knockout of cryptochromes activates constitutively proinflammatory cytokine expression and the innate immune system gets hypersensitive (15). The knockdown of CRY2 in specific leads to up-regulation of genes contributing to inflammation and to immune responses, and the proinflammatory cytokine activity through the actions of interleukin-6 and interleukin-18 is increased (16). Cryptochromes also inhibit the G protein coupled receptors activity through a direct interaction with the G(s)alpha subunit (17).

By these mechanisms, the cryptochromes might protect the individual from a depression-like state seen in conditions where dysfunction in control of the mesolimbic dopaminergic tracts leads to increased cyclic adenosine monophosphate production and increased depression-like behaviour (18). Furthermore, mice displaying higher trait-anxiety behaviour and co-morbid depression-like behaviour have lower expression levels of *Cry2* in specific in the hippocampus than normal anxiety/depression-like behaviour mice (19). This finding tells us that dysfunction of the circadian clock links to depression-like behaviour at the genetic level and points towards a key role for CRY2 protein.

The loss of cryptochromes does change physiology, and dysfunction of cryptochromes may change as well. *CRY2* appears to be a "mood gene" (20). Of the two cryptochromes, CRY2 has the power of balance, since it not only acts as a general repressor, but also opposes in specific the actions of CRY1, denying CRY1 access to DNA targets too early (21). This is one of the factors that needs to be kept in mind when a plan of development of cryptochrome activators or inhibitors (22-23) to be used for treatment of mood disorders is made. At last, there is light at the end of the tunnel.

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