SMGroup

SM Journal of Depression Research and Treatment

Mini Review

My Brain is on a 24/7 Schedule

Luisa V. Lopes* and Joana E. Coelho

Instituto de Medicina Molecular da Faculdade de Medicina de Lisboa, University of Lisbon, Portugal

Abstract

The impact of a "24-7" schedule in our general physiology, as well as our cognitive capacities, is a growing social concern. A disrupted circadian rhythm is inherent to many occupations in today's society, namely airline pilots and crew-members, military and law enforcement personnel, medical staff or any rotating shift worker. This makes it a socially pervasive phenomenon, taking a toll on mental and general health. The comprehension of these mechanisms has been delayed by the difficulty to dissociate the effect of sleep abnormalities from circadian clock dysfunction and the lack of indisputable biological markers to define and diagnose a circadian disorder.

Article Information

Received date: Aug 07, 2015
Accepted date: Nov 02, 2015
Published date: Nov 17, 2015

***Corresponding author**

Luísa V. Lopes, Instituto de Medicina Molecular, Egas Moniz, 1649-028 Lisboa, University of Lisbon, Portugal, Tel: + 35121 7985183; Fax: + 35121 7999454; Email: lvlopes@medicina.ulisboa.pt

Article DOI 10.36876/smjdrt.1009

OPEN ACCESS

ISSN: 2573-3389

The Clock is Ticking

Circadian rhythms - physiological and behavioral cycles with a periodicity of approximately 24 h—are generated by an endogenous biological clock, the Suprachiasmatic Nucleus (SCN). Any disruption of this system can negatively affect sleep quality, alertness, cognitive performance, motor control, mental health and metabolism [1]. The hypothalamus functions as a central regulator of metabolism and energy use, by coordinating the physiological responses of the entire organism through hormonal signaling. Such hypothalamic regulation is now seen as a very strong candidate to a role in cognitive decline during brain aging: the hypothalamus coordinates stress responses, in part through the regulation of peripheral Glucocorticoid (GC) secretion [10]. GCs can be sensed directly by another part of the brain, the **hippocampus - crucial for learning and memory** - which then suppresses hypothalamic stimulation of further GC release in a negative feedback loop. Excessive GC production associated with chronic or severe stress may impair hippocampal neuronal function and predispose the organism to neurodegeneration [11], potentially disrupting the regulatory circuit that connects the hippocampus and the hypothalamus. Release of cortisol from the adrenal cortex is under tight regulation of this hypothalamic–pituitary–adrenal (HPA) axis. Many of these functions become impaired in neurodegenerative disorders such as Alzheimer disease (AD), Parkinson disease (PD) and Huntington disease (HD), in which several brain areas—including the nuclei involved in circadian and sleep regulation—are affected by neurodegenerative processes. It is not surprising, therefore, that these disorders often entail progressive breakdown of the normal cycles of rest– activity, sleep and alertness; *however, it remains to be clarified whether disruption of circadian rhythms could also be involved in driving the disease process itself.*

In humans, cognitive impairments associated with shift work call attention to the importance of such synchronization [3]. The mechanisms underlying circadian rhythms involve circadian oscillations in gene expression, in protein modifications and hormone secretion. Experiments in model organisms in which single or multiple clock genes have been deleted or mutated have revealed genes that are critically important for circadian rhythms in locomotion, behavior, physiology and gene expression, such as *Per2, Per3, DBP, Bmal1, Nspas2, Nrd1 and Nrd2* [1,4]. Current models connect these circadian clock genes and their products in transcriptional–translational feedback loops [5]. *However, cognitive loss associated to aging is not entirely explained by disruption of the circadian clock induced by mutations.*

Although it is sometimes difficult to dissociate the effect of sleep abnormalities on cognition and mood from circadian clock dysfunction, a growing body of evidence indicates that the involvement of the circadian clock in the regulation of cognition and mood is far beyond the circadian control of sleep and the rest–activity cycle.

An aging-related decline in spatial, declarative and other forms of memory is well documented (our own data [6-8] and reviewed in [2]). Furthermore, changes in mood regulation, for example, increased frequency of episodes of depression, mania and anxiety, are also observed with age [9]. In many cases, the cognitive disruption may be secondary to compromised neural circuitry in the brain regions regulating output rhythms. *The current challenge is to establish whether circadian system disturbances contribute to age-related memory loss* [4,5], *or whether they are merely symptomatic of the disease process.*

Novel Drugs to Restore Central Glucocorticoid Balance

It is now very clear that hippocampus plays a crucial role in regulating the HPA axis [14];

and chronic exposure to glucocorticoids leads to cell death and hippocampal atrophy [13,14]. Impaired cortisol levels are observed in post-traumatic stress syndrome or major depression [25]. Increased glucocorticoid activity has also been associated with greater hippocampal atrophy and memory impairment in the elderly [15]. This is probably consequence of dendritic retraction and hippocampal dysfunction that we have shown to occur under these conditions [11].

We have recently revealed that age-related disorders are associated to down regulation of Glucocorticoid Receptors (GR) in the hippocampus, and consequent desensitization of the regulatory feedback to the hypothalamus [11]. Accordingly, in a large study of elder humans aged 50–70 years, elevated salivary levels of cortisol were found to be correlated with poor cognitive function across a broad range of domains including language, processing speed, eye-hand coordination, executive function, verbal learning, and memory and visual memory [16]. Also, higher cortisol levels have been associated with more rapid AD disease progression [17], and systemic administration of glucocorticoids or stress shown to potentiate memory impairments, hippocampal damage, β-amyloid formation and Tau accumulation in transgenic AD mice [18-20]. Furthermore, primary hippocampal degeneration in individuals with AD may also disrupt hippocampal–hypothalamic control of systemic physiological functions [12].

We have been studying the interesting ability of novel adenosine-based drugs to rescue age-like memory deficits and anxiety in rodents, by re-establishing central Glucocorticoid Receptor (GR) levels, hippocampal feedback and consequent control of systemic CORT circadian levels [11,23]. However, proof of a direct link between GR and age-related cognitive loss was lacking until very recently. This gap was closed by different groups that independently reported that reestablishing CORT oscillations on one hand; and blocking GR on the other hand, rescued memory deficits in AD mouse models [21,22].

Taken together, these evidences strongly suggest that the circadian dysfunction is a multifactorial condition associated to age-related cognitive loss. However, rather than being only secondary to age-related neurodegeneration, it is now becoming clear that it can itself drive cognitive decline. In our view a more objective and systematic approach to test this hypothesis is needed. This is now becoming possible with the novel, minimally invasive and highly sensitive tools at our disposal. Those in the field must strive to search for an objective definition of human endophenotype for circadian disorders, to clearly identify the circadian players in cognitive dysfunction and finally, to validate these mechanisms in cognitive impaired patients with known circadian disturbances. We believe that the possibility of establishing the pattern of clock gene expression and hormone oscillations in patients, the use of functional MRI to diagnose of hypothalamus-hippocampus feedback control [24], and the novel and more reliable ways of associating activity/sleep to cognitive performance will definitely push the chronobiology forward.

By identifying circadian modulators with impact on cognition, and developing new tools to monitor such impact, it will be possible lay the ground for new strategies to ameliorate the effects of the '24-7' schedule on modern societies, thereby promoting truly science-based healthy aging strategies.

References

1. Mohawk JA, Green CB, Takahashi JS. Central and peripheral circadian clocks in mammals. Annu Rev Neurosci. 2012; 35: 445-462.
2. Kondratova AA, Kondratov RV. The circadian clock and pathology of the ageing brain. Nat Rev Neurosci. 2012; 13: 325-335.
3. Kyriacou CP, Hastings MH. Circadian clocks: genes, sleep, and cognition. Trends Cogn Sci. 2010; 14: 259-267.
4. Ko CH, Takahashi JS. Molecular components of the mammalian circadian clock. Hum Mol Genet. 2006; 15: R271-277.
5. Shearman LP, Sriram S, Weaver DR, Maywood ES, Chaves I, Zheng B, et al. Interacting molecular loops in the mammalian circadian clock. Science. 2000; 288: 1013-1019.
6. Lopes LV, Cunha RA, Ribeiro JA. Increase in the number, G protein coupling, and efficiency of facilitatory adenosine A2A receptors in the limbic cortex, but not striatum, of aged rats. J Neurochem. 1999; 73: 1733-1738.
7. Sousa VC, Vital J, Costenla AR, Batalha VL, Sebastião AM, Ribeiro JA, et al. Maternal separation impairs long term-potentiation in CA1-CA3 synapses and hippocampal-dependent memory in old rats. Neurobiol Aging. 2014; 35: 1680-1685.
8. Diógenes MJ, Costenla AR, Lopes LV, Jerónimo-Santos A, Sousa VC, Fontinha BM, et al. Enhancement of LTP in aged rats is dependent on endogenous BDNF. Neuropsychopharmacology. 2011; 36: 1823-1836.
9. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. Nature. 2010; 464: 529-535.
10. Jankord R, Herman JP. Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. Ann N Y Acad Sci. 2008; 1148: 64-73.
11. Batalha VL, Pego JM, Fontinha BM, Costenla AR, Valadas JS, Baqi Y, et al. Adenosine A2A receptor blockade reverts hippocampal stress-induced deficits and restores corticosterone circadian oscillation. Mol Psychiatry. 2013; 18: 320-331.
12. Bao AM, Meynen G, Swaab DF. The stress system in depression and neurodegeneration: focus on the human hypothalamus. Brain Res Rev. 2008; 57: 531-553.
13. Sapolsky RM. Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. Exp Gerontol. 1999; 34: 721-732.
14. Knoops AJ, Gerritsen L, van der Graaf Y, Mali WP, Geerlings MI. Basal hypothalamic pituitary adrenal axis activity and hippocampal volumes: the SMART-Medea study. Biol Psychiatry. 2010; 67: 1191-1198.
15. Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci. 1998; 1: 69-73.
16. Lee BK, Glass TA, McAtee MJ, Wand GS, Bandeen-Roche K, Bolla KI, et al. Associations of salivary cortisol with cognitive function in the Baltimore memory study. Arch Gen Psychiatry. 2007; 64: 810-818.
17. Csernansky JG, Dong H, Fagan AM, Wang L, Xiong C, Holtzman DM, et al. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am J Psychiatry. 2006; 163: 2164-2169.
18. Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. J Neurosci. 2006; 26: 9047-9056.
19. Caroll D, Zhang B. Primer and interviews: advances in targeted gene modification. Interview by Julie C. Kiefer. Dev Dyn. 2011; 240: 2688-2696.
20. Yao YY, Wu QS, Li WZ, Li WP. Dexamethasone potentiated AÎ²-induced learning and memory impairment in rats. Neurol Res. 2011; 33: 371-380.
21. Laurent C, Burnouf S, Ferry B, Batalha VL, Coelho JE, Baqi Y, et al. A2A adenosine receptor deletion is protective in a mouse model of Tauopathy [Internet]. Mol Psychiatry. 2014: 1-11.

Citation: Lopes LV and Coelho JE. My Brain is on a 24/7 Schedule. SM J Depress Res Treat. 2015; 1(2): 1009.
https://dx.doi.org/10.36876/smjdrt.1009

22. Lante´ F, Chafai M, Raymond EF, Pereira AR, Mouska X, Kootar S, et al. Subchronic Glucocorticoid Receptor Inhibition Rescues Early Episodic Memory and Synaptic Plasticity Deficits in a Mouse Model of Alzheimer's Disease. Neuropsychopharmacol. 2015; 40: 1772-1781.

23. Coelho JE, Alves P, Canas PM, Valadas JS, Shmidt T, Batalha VL, et al. Overexpression of Adenosine A2A Receptors in Rats: Effects on Depression, Locomotion, and Anxiety. Front Psychiatry. 2014; 5: 67.

24. Lovallo WR, Robinson JL, Glahn DC, Fox PT. Acute effects of hydrocortisone on the human brain: an fMRI study. Psychoneuroendocrinology. 2010; 35: 15-20.

25. Gerritsen L, Comijs HC, van der Graaf Y, Knoops AJ, Penninx BW, Geerlings MI. Depression, hypothalamic pituitary adrenal axis, and hippocampal and entorhinal cortex volumes--the SMART Medea study. Biol Psychiatry. 2011; 70: 373-380.

Citation: Lopes LV and Coelho JE. My Brain is on a 24/7 Schedule. SM J Depress Res Treat. 2015; 1(2): 1009.
https://dx.doi.org/10.36876/smjdrt.1009