Rhythmic dopamine: new emerging role of the pleasure molecule

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Science is a long, labor-intensive process through which the majority of inventions take years to develop. Yet, sometimes major breakthroughs emerge from unexpected sources or even apparent mistakes. The history of science is rich with such examples of serendipities [1]. Such was the case for the story behind our study published early this year in PlosOne [2]. We have been using infrared captors to monitor the general locomotor activity of individually housed Non-Human Primates (NHP) when we noticed something odd. One of the animals treated with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) 7 months earlier in order to induce a degeneration of Dopamine (DA) neurons (which is the main neuropathological feature of Parkinson’s disease) showed a complete behavioral arrhythmia with a continuous activity day and night over 11 days without a consolidated phases of sleep and wakefulness. At first, we thought the infrared captor monitoring the behavioral activity of that animal ceased to function properly, especially when we noticed that other animals from the same colony displayed a normal behavioral rest/activity pattern. Upon verification, this however was not the case. Rather what triggered this abnormal behavior in the MPTP-treated animal was a continuous 24-hours light paradigm accidentally generated by a technician while fixing an independent issue within the experimental room housing the animals.

NORMAL BODY CLOCK FUNCTIONING

This surprising result catalyzed the initiation of a study that aimed to investigate the underlying mechanism of the potential circadian alterations in Parkinson’s disease (PD). We first tried to replicate the same findings in other animals. Indeed, after MPTP treatment of a set of additional animals, alterations of the 24-hour temporal organization of rest/activity rhythm ranging from a poorly consolidated daytime activity of extremely low amplitude to a complete loss of the circadian rhythm city emerged when the animals were housed in continuous constant light conditions. Interestingly, the switch of the lightning condition to a 12h light/12h dark (LD) paradigm restored an apparently normal nycthemeral rhythm with a significant 24h periodic component. These results suggest that transitions between light and dark phases under LD cycle masked the expression of the abnormal behavioral arrhythmia induced by the lesion of DA neurons following MPTP insult.

The circadian alterations displayed by MPTP-treated NHP models of PD are reminiscent of the behavioral alterations after inactivation of the central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus in both rodents and NHP [3]. To test whether the same underlying pathophysiology (SCN dysfunction) account for the behavioral arrhythmia observed in MPTP-treated NHP, we assessed the profiles of cortisol and melatonin hormonal rhythms which are both driven, independently of the rest/activity cycle, by the same endogenous clock in the
SCN. The results of these assays were as surprising as was our original finding. Both the amplitude and the phase angle relationships of cortisol, melatonin and rest/activity rhythms were unaffected by MPTP treatment. These results imply that the molecular machinery of the SCN clock was still functioning properly and that a different mechanism, other than SCN dysfunction, was behind the behavioral arrhythmia precipitated by MPTP treatment.

NEW EMERGING ROLE OF DOPAMINE

While our study was still ongoing, a study investigating the role of DA in the regulation of clock gene expression was published by Amir and his colleagues from Concordia University in Montreal [4]. In that study, the authors used another toxin (6 hydroxy-dopamine) to deplete rat’s brain from DA and showed that the daily profile of clock genes was blunted selectively in the dorsal striatum – a region of the brain involved, among other physiological functions, in the control of motor behavior. The authors then succeeded in restoring a normal 24h pattern of clock gene expression in the same striatal region using timed pharmacological activation of the DA system. Interestingly, none of their lesional and pharmacological manipulations affected clock gene expression in the SCN [4]. In what seems to be a follow-up study, the same team assessed the rest/activity behavior of 6 hydroxy-dopamine treated rats and showed that the circadian rhythmicity of the rest/activity cycle was disrupted following DA depletion [5]. All these findings corroborate perfectly with our results in the MPTP-treated NHP and prompted us to propose a model in which DA would be responsible for the transduction of the circadian signal from the SCN to brain structures controlling motor functions (i.e. striatum). According to this model, the degeneration of DA neurons would lead to a disconnection between the endogenous SCN clock and the neural network controlling coherent circadian rest/activity cycle and eventually to the fragmentation of rest/activity behavior (Figure 1).

TRANSLATIONAL INSIGHTS TO NEURODEGENERATIVE DISEASES

Mounting evidences have been built over the last 10 years for a link between sleep fragmentation and multiple neurodegenerative diseases [12]. In Parkinson’s disease for
example, alterations in the day/night activity pattern may precede the emergence of the hallmark motor symptoms and will inevitably worsen over disease progression. Two physiological processes have been emphasized for the regulation of sleep/wakefulness behavior. The circadian SCN-based oscillator which is responsible for the consolidation of sleep and wakefulness into distinct phases and a homeostatic process which monitors and reacts to the need of sleep depending on the quality and quantity of prior sleep and wakefulness. In order to study how the circadian process modulates sleep behavior in humans, the most reliable procedure is to release subjects into a forced desynchrony which involves a forced 28 h sleep/wake cycles under controlled conditions with a suppression of all potential time cues. Because normal people cannot entrain to this protocol, it is possible to assess the effect of circadian time on sleep and other physiological functions. Unfortunately, these kinds of experiments were never, and are unlikely to be, conducted with PD patients for ethical reasons related to withhold treatment from disabled patients. However, equivalent environmental conditions in which the circadian system is challenged do exist in nature. Our hypothesis, if true, would predict that in northern latitudes where PD patients are exposed seasonally to continuous day or night conditions, alterations in the 24 h organization of the sleep/wakefulness behavior would be significantly exacerbated during summers and winters. Although such direct evidence is still lacking, epidemiological studies have revealed, a still unexplained, high occurrences of PD in northern compared to tropical latitudes. We propose that the loss of the circadian modulation of DA availability in the brain of PD patients as a consequence of DA neuron degeneration would be the pathophysiological correlate that could explain such trends. The next obvious step towards the confirmation of this hypothesis will be to assess the circadian pattern of sleep in a large number of PD patients settled at different latitudes and link the potential alterations of sleep/wake rhythm with biological markers of DA rhythmicity using for example fMRI and PET technologies. Meanwhile, testing the hypothesis will still depend on the use of animal models of PD as it would involve the assessment of sleep and circadian rhythms under unnatural constant dark or light conditions after specific interference with the DA neurotransmission.

The concept of the circadian modulation of DA concentration in the brain has also direct relevance to the efficiency of L-DOPA therapy in PD. Since its discovery in the mid-1950, L-DOPA is still the mainstay of PD therapy. Unfortunately, most patients show mild to severe dyskinesia following long-term L-DOPA intake. Extensive studies have been done, and are still ongoing, in order to unravel how and why L-DOPA therapy leads to such debilitating side effects. The prevailing explanation of these undesirable effects of L-DOPA treatment is the non-physiological fluctuations of DA levels in the striatum of PD brains. In normal conditions, striatal DA concentrations are maintained at fairly constant levels with significantly higher concentrations during the active phase. In PD patients, degeneration of DA fibers in the striatum renders striatal DA levels dependent on the peripheral availability of L-DOPA. Because the current standard oral L-DOPA formulations involve intermittent dosing, the resulting fluctuations in the plasmatic DA levels are translated into abnormally fluctuating striatal DA concentrations. Additionally the disconnection between the SCN and the striatum following DA neuronal degeneration will lead to the loss of the circadian modulation of striatal DA levels. Consequently, this non-physiological oscillations of DA levels results into pulsatile stimulation of DA receptors during inappropriate time of the day especially when L-DOPA is taken just before bedtime (which is usually the case). As a consequence of this ‘chaotic’ stimulation of DA receptors, abnormal changes in gene, molecular and firing pattern develop in striatal neurons resulting inevitably in the development of motor complications. In a series of studies published by a team of neurologists headed by Warren Olanow from Mount Sinai School of Medicine in New York, the benefit of continuous delivery of L-DOPA over the waking hours of the day was investigated in PD patients. In their recent double-blindly controlled study published 9 months ago in the Lancet neurology, Olanow and colleagues used a newly developed Duodopa – a stable solution of L-DOPA which is administrated within the jejunum through a surgically inserted trans-abdominal port connected to an external pump – to infuse constant concentration of L-DOPA during the waking hours of the 24h. Interestingly, this protocol was associated with significant improvement of daily living with more than 4h overall reduction in motor complications compared to standard oral intake protocols. The beneficial effects of this new approach of L-DOPA intake extend also to other physiological functions. Few years ago, Olanow team showed also that protocols in which L-DOPA was infused only during waking hours prevented the emergence of serious psychiatric problems usually experienced by patients receiving round-the-clock 24h infusions. These observations provide strong evidence for the functional importance of both the continuous stimulation and the circadian modulation of DA neurotransmission to yield better clinical outcomes.

CONCLUSION

Since its identification as a biologically active molecule of its own in the brain, DA has been implicated in a variety of biological processes including motor control, attention,
rewards and modulation of high cognitive functions. During the last few years, we have witnessed the building-up of cumulative evidences for the involvement of DA in the modulation of circadian rhythms. The implications of this new emerging role of DA have already reached the clinic. Although this is a promising start towards improving the quality of life of many patients suffering from Parkinson’s disease, more research is needed to further understand the interactions between DA and the circadian system. Hopefully then, the translational benefits could be extended to other medical diseases involving DA dysfunction such as Huntington disease, drug addiction, schizophrenia and attention deficit hyperactivity disorder.

References