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Short Commentary

Effect of chronic circadian disorder during pregnancy on progeny mice

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Abstract

Circadian rhythms are very important to the reproduction [1, 2], development [3, 4] and physiological activities of autonomic nerve innervation of mammals and can even be said to be: Time is everything. Here is a short communication about 'Environmental perturbation of the circadian clock during pregnancy leads to transgenerational mood disorder-like behaviors in mice' which we published in 2017. At the same time, some interesting scientific questions will raised up, which are also the next step of our research.

Keywords: Circadian rhythms, perturbation, rhythmic disorder

Circadian rhythms are very important to the reproduction [1, 2], development [3, 4] and physiological activities of autonomic nerve innervation of mammals and can even be said to be: Time is everything. Here is a short communication about 'Environmental perturbation of the circadian clock during pregnancy leads to transgenerational mood disorder-like behaviors in mice' which we published in 2017. At the same time, some interesting scientific questions will raised up, which are also the next step of our research. In the study of the relationship between circadian rhythm and various diseases, mental disease is not a popular direction. Some studies have found a strong link between the rhythm of master clock, SCN, and a variety of mental disorders, like bipolar and depression disorder [5-8]. A large proportion of patients with major depression disorder, anxiety and bipolar disorder are accompanied by varying degrees of sleep-arousal disorder [9,10]. Even the first symptom of some patients with mental illness is sleep-arousal disorder [11]. But it is difficult to identify the causal relationship between mental disorder and circadian disorder. Although our research is not sufficient to clarify the relationship between the two. Our findings may have some implications for this: they may be causally related to each other. Many articles reported that chronic restraint stress or chronic unpredictable stimulation in pregnancy can cause abnormal behavior of offspring mice or rats similar to mental disorders [12-14]. On the other side, the abnormal circadian rhythms were found in the detection of SCN circadian rhythm in MDD model rats and mice [15,16]. Based on these backgrounds, our initial assumption was: would it be possible to induce depression or anxiety in mice if they were stimulated by a single rhythmic disorder? However, it was found that frequent switching circadian rhythms did not induce significant behavioral abnormalities in adult mice (forced swimming and sugar water preference experiments). So, what about the effect on the offspring? Then we designed frequent circadian rhythms of maternal mice during pregnancy. The results showed that offspring mice had subculture abnormal behavior (at least 1 generation). At this point, we found that rhythm disorder can be the cause of mental disorders. Embryonic development is a rigorous and orderly stage of spacetime development the timeline is a crucial rule in this development, and once the schedule is broken, it can have a fatal effect on the embryo in which organisms undergo programmed changes in fixed time and space. We can imagine that mammalian embryos cannot directly perceive light signals in the environment of the mother undefined womb, but only through the mother undefined neural fluid to regulate the passive acceptance of the timing signal. Although we know that the programmed spatiotemporal expression patterns of embryonic development are determined by genes, However, abnormal maternal changes, such as changes in the levels of nerve, body fluids and hormones caused by abnormal rest, feeding time, and the state of psych sperm, are both stress states for both embryos and embryos. This stress state is likely to lead to an increase in the incidence of gene mutations and the effect of epigenetic levels in embryos. Once this effect occurs, it may involve not only a single organ, but also a wide range of multiple systems. Therefore, we confirmed that the difference protein did involve multiple systems and biological functions after the protein differential spectrum was detected in the hypothalamus of children with chronic rhythm disorder during pregnancy. We tested the expression of MC4R, one of the differential proteins. And it was found that there was not only significant difference between NS and CCD mice, but also has gender difference in CCD-F1 mice. This has aroused our concern about the cardiovascular system and sexual development of the offspring after CCD.

MC4R is, which is G protein-coupled receptors that stimulate adenylate cyclase, one of five melanocortin receptors (MCRs)（MC1RMC5R）[17-20]. MC4Rs are mainly present in the central nervous system (CNS). Melanocortins responds to stress [21], and melanocortins regulate several physiological functions, including body weight, sexual behavior, and

cardiovascular function [22-29]. The research indicated that α-MSH microinjections into the nucleus ambiguous exert excitatory effects on parasympathetic preganglionic nucleus ambiguous neurons via MC4Rs, leading to bradycardic responses. [30]. We spontaneously thought that do CCD-F1 mice has abnormal phenotypes in cardiovascular activity? It there a sexual dimorphism? Therefore, we observed the CCD-F1 generation mice of different genders. According to the experimental results obtained at present, CCD-F1-female has obvious abnormal puberty development, which is characterized by delayed vaginal opening time and disorder of estrous cycle. The phenotypes of CCD-F1-male were mainly found in the increased susceptibility to arrhythmias. Under the same dose of drug induction, fatal arrhythmias were more likely to occur (ventricular fibrillation, mortality rate was much higher than that of non-stressed F1 generation). We will continue to study these two interesting phenomena. We hope that our results can further understand the regulation of daily rhythm on the development and function of different tissues and organs.

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