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Opinion

Winding Up the Internal Circadian Clock and Preterm Ductus

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Abstract

The circadian system regulates many aspects of physiological functions in human body and requires a delicate interplay between suprachiasmatic nucleus, pineal gland, melatonin and clock genes. Maturation and synchronization of the fetal circadian system is mostly governed by maternal master clock and needs a complete and uncomplicated intrauterine life. Premature birth is being born not only with underdeveloped organ systems, but also with deprivation of this preparation period. Currently there is no proven association between ductal closure and circadian system, however there are clues that clock genes can affect vascular morphogenesis and function. With better understanding the cyclic environment in utero, we can have an opportunity to modify our current strategies in neonatal care. Preterm ductus may really have an internal clock that needs to be wounded in order to be properly programmed for closing.

Keywords: *Circadian Rythms; Melatonin; Preterm İnfant; Patent Ductus Arteriosus*

Famous Japanese novelist Haruki Murakami describes an imaginary bird which winds the spring of the world in one of his novels. This is so called ''wind-up bird'', comes to the narrator's yard every morning to wind his quiet little world with its unique voice. Only the real wind-up bird could make this kind of sound, (just like a particular starting signal) so that, the only one that is able to wind the world's spring the way it was supposed to be, was this exclusive bird [1].

Sure enough, there is an actual circadian clock in human beings that drives the endogenous rythms of our lives. This circadian system not only plays a role in the measurement and interpretation of day length and time, but also involves in cardiovascular function and circulation, patterns of blood pressure and body temperature, hormone release and immunity. The rhythm is closely linked to the light-dark cycle and requires a delicate interplay between suprachiasmatic nucleus, pineal gland, melatonin and clock genes [2,3].

In a growing human fetus, this clock is underdeveloped yet, and the circadian rythm of the fetus is mostly governed by maternal master clock. However, although the internal clock of the fetus is not fully functioning, during ongoing pregnancy, it is continuously being programmed to work properly alone after birth. Maturation and synchronization of the fetal circadian system requires a complete and uncomplicated intrauterine life. Fetus is exposed to mothers melatonin although there is no light-dark cycle in utero. Maternal melatonin, crosses placental barrier and influences the expression of fetal clock genes. Rythmic fluctations of serum levels of maternal melatonin provide light-dark and time information for the fetus and fetus displays a similar rythmicity with the mother. In addition to melatonin, rythmic fluctuations of cortisol and regular repeats of feeding times of the mother constitutes a cyclic environment which programmes the fetal clock. In other words, the rythmicity of maternal hormones constitutes the the proper signal for winding up the babies internal clock. By the birth following an uncomplicated pregnancy, this clock which has been winded, starts to work properly [3].

Premature birth is not only beeing born underdeveloped organ systems, but also with deprivation of this rythmicity, premature ending of this preparation period, in other words ''winding of the clock is not adequate''. Besides, many stimuli during neonatal intensive care does not support the maturation of this internal clock. Absence of day-night life cycles, interrupted sleep and awake periods due to procedures and many noxious stimuli like pain contribute negatively to maturation of the circadian sytem in preterm infants.

Currently there is no proven association between ductal closure and circadian system. However there are clues that clock genes can affect morphogenesis and function [4]. As well as vasoconstriction, vascular remodeling is the pivotal point for definitive ductal closure which involves migration of smooth muscle cells into subendothelium and platelet vessel Wall interaction [5]. Both vascular tone and thrombus formation have been shown to diplay diurnal variation [4]. Moreover, there are evidences of existence of circadian clock elements in vascular smooth muscle cells and fibroblasts [4]. A rhythmic oscillation in gene expression of clock components in mouse aorta has recently been shown which is found to be in alignment with the master oscillator in the suprachiasmatic nucleus [4].

Interestingly, phototherapy has been shown to be associated with ductal patency [6] which occurs via a pathway other than PGE2 or PGI2 [7] and chest shielding did not prevent ductal patency [7]. Perhaps this association may also be explained with the concept of light mediated chronodistruption.

With better understanding the cyclic environment in utero, we will have an opportunity to modify our current strategies in neonatal care. Rendering the similar rythmicity with biologic oscillators during intensive care period will support the development of the internal clock of preterm infants and can provide the correct local microenvironment to achieve closure of patent ductus arteriosus. For example, a rythmicity can be provided by pulsatile hormonal support or pulsatile increament in infusion rate of parenteral nutrition elements mimicing maternal postprandial state. Since melatonin is excreted in breast milk [3], collecting the milk expressed at night time seperately and feeding the baby with this milk during night can have some effect. Likewise, oscillations in environmental temperature, sound and light, and maybe filtering certain wavelenghts of light [8] in order to prevent chronodistruption can also emerge as new supportive strategies in the future. Preterm ductus may really have an internal clock that needs to be wounded in order to be properly programmed for closing.

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