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Heart-rate changes in asphyxic preconditioning in rats depend on light-dark cycle

Research Article

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Abstract: Generally, it is assumed that heart-rhythm disorders during hypoxia result from the interplay between the autonomic nervous system (ANS) and the direct effect of hypoxia on cardiorespiratory structures of the central nervous system and on the myocardium. Circadian variability in the ANS may substantially influence the electrical stability of the myocardium, and thus it is associated with the preconditioning protective mechanism. We designed our study using anaesthetized Wistar rats (ketamine/xylazine 100 mg/15 mg/kg, i.m., open chest experiments) to evaluate the effect of preconditioning (PC) induced by 1 to 3 cycles (1 PC-3 PC) of asphyxia (5 min. of artificial hypoventilation, VT = 0.5 ml/100 g of b.w., 20 breaths/min.) and reoxygenation (5 min. of artificial ventilation, VT = 1 ml/100 g of b.w., 50 breaths/min.) on the heart rate (HR) during followed exposure 20 minutes of hypoventilation after adaptation to a light-dark (LD) cycle of 12 hours:12 hours. Hypoxic HR increases were only minimally prevented by 1 to 2 PC pre-treatment, particularly during the dark part of the day. A statistically significant HR increase required 3 PC and was seen only in the light part of the day. We concluded that possible ANS participation in asphyxic preconditioning depends not only on the number of preconditioned cycles but also on the LD cycle, when the ANS participation in preconditioning can be effective only in the light (nonactive) period.

Keywords: *Chronophysiology • Heart rate • Preconditioning • Asphyxia*

1. Introduction

Cyclic fluctuations in cardiovascular responses on a subdiurnal, circadian, or supradian basis are constituted by the short-term and long-term variabilities in the autonomic nervous system (ANS). Previous data have shown that daily rhythmicity in the tone of sympathetic and parasympathetic nerves in healthy organisms is paralleled by corresponding changes in the electrophysiological properties of the myocardium [1]. Circadian variability in the ANS may also substantially influence the electrical stability of the myocardium under pathological conditions, including systemic hypoxia, pulmonary hypoventilation, asphyxia, or acidosis [2-4].

It is assumed that both the hypoxic changes in the phasic and tonic drive from the ANS and the alterations in the sensitivity of the myocardium to autonomic nervous drive may also be involved in the effect of preconditioning. This mechanism of cardioprotection against a subsequent ischemia or reperfusion injury has been achieved on isolated perfused hearts by brief periods of myocardial ischemia followed by reperfusion [5-7]. It is now apparent that protection from ischemic preconditioning spreads from distant organs to the heart [8,9] possibly via activation of the ANS [8,10-12]. It is possible that release of local triggers of ischemic preconditioning activates the ANS either directly [11,12] or via sensory nerves [13-15] and transfers the signal to the myocardium or other remote tissues.

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Evidence exists that sympathovagal regulation may be related to the ischemic preconditioning protective mechanism [16,17]. Ischemic preconditioning is mediated by the release of sympathetic neurotransmitters and stimulation of α_1-adrenergic receptors [18,19]. Acetylcholine, the parasympathetic mediator, is also involved in the ischemic preconditioning triggering process [19]. The anti-arrhythmic protection afforded by ischemic preconditioning may be mediated by preservation of autonomic function [20]. Other evidence implies that ischemic preconditioning may affect sympathovagal activity from the initial effect to the target effect [21,22]. Brief coronary occlusion may result in severe autonomic reaction, as measured by reduced heart-rate variability; however, the autonomic reaction after further coronary occlusion has been shown to be statistically significantly smaller [22-24]. These phenomena imply the importance of cardiac autonomic regulation in the ischemic preconditioning protective process.

These results strongly indicate probable ANS participation in cardioprotection induced by ischemic preconditioning. Although preconditioning by hypoxia is less studied, it is known that pretreatment by repetitive episodes of systemic hypoxia or hypoventilation-induced asphyxia under in vivo conditions has evoked not only similar cardioprotective effects [25] but also has shown marked light-dark dependence [26]. Currently, the data regarding ANS participation in hypoxic preconditioning and, especially, dependence on periodicities in the environment are absent.

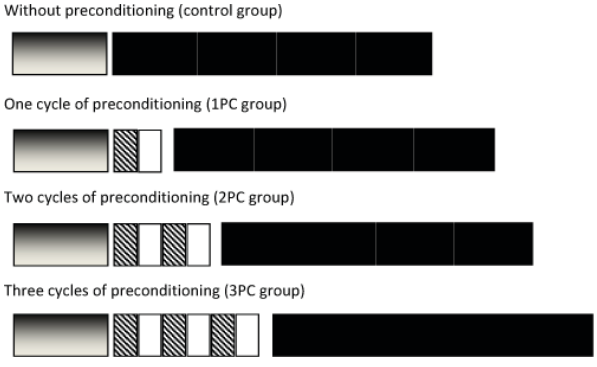
We hypothetized that if the ANS participates in cardioprotection induced by ischemic preconditioning, it also participates in the process of hypoxic preconditioning, and then, if the ANS plays a role in hypoxic preconditioning, the effect would depend on external periodicity because cardiovascular and autonomic nervous functions show a dependence on the 24-hour period. Thus, the aim of this chronophysiological study was to examine the effect of adaptation of the light-dark cycle on heart-rate responses, parameter refering to autonomic drive, during the post-anaesthetic state, hypoventilatory hypoxia, and cardiac preconditioning induced by repeated asphyxia in vivo.

2. Material and Methods

The experiments were performed in anaesthetized (ketamine/xylazine anaesthesia, ketamine 100 mg/kg Narkamon, Prague + xylazine 15 mg/kg Rometar Prague, i.m.) female Wistar rats (3 – 4 months old). The studies conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and were approved by the local ethics committee of the Medical Faculty, University P.J.Šafarik in Košice (number of permission 2/05). On completion of the experiments, the animals were euthanized by the cardiac administration of a ketamine overdose. Anaesthesia was maintained such that painful stimuli and surgery did not evoke noticeable motor or cardiovascular responses.

Scheme 1. Adaptation of rats to the light-dark cycle 12 hours:12 hours in a special room (humidity 50 – 60%, temperature in cages 24 0C) for 4 weeks. Light part of the day – empty stripes; dark part of the day – black stripes. Arrows indicate the running time of the experiment.

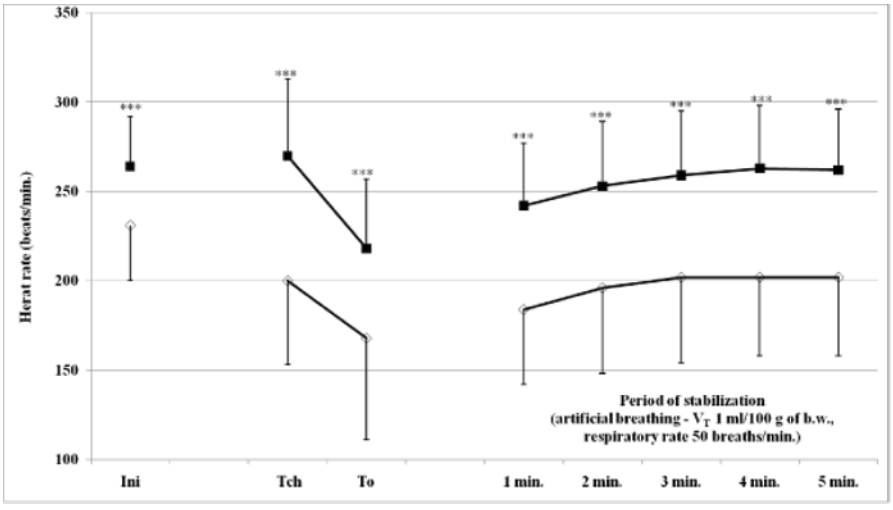
Scheme 2. Protocol of preconditioning by systemic asphyxia. The black-white stripes – initial phase of experiments, with heating of animals to rectal temperature measured before the application of the anaesthetic agent, tracheotomy, thoracotomy, stabilization; hatched stripes – preconditioning cycles by systemic asphyxia; empty stripes – reoxygenation; black stripes – 20 minutes of hypoventilation.



The effect of the light part of the day on the changes in heart rate was monitored after adaptation of animals to a light-dark (LD) cycle of 12 hours:12 hours for 4 weeks, with the dark part of day from 18.00 to 06.00 hours. The experiments were performed twice (on the first animal between 09:00 – 10:00 and on the second one between 12:00 – 13:00 h). The effect of the dark part was monitored after an inverse setting of the LD cycle, with the dark part from 06:00 to 18:00 h, with the experiment time as in the first case (Scheme 1).

The animal were divided into 4 experimental groups for the light and dark periods. The first group of animals was without preconditioning (n = 12 light, n = 19 dark), and the other three experimental groups were preconditioned

Figure 1. The average heart rate (HR) values ± SD before, during, and after the surgical interventions in the light (empty rhombus) and dark (black square) parts of the rat regimen day. Ini – intact; Tch – after tracheotomy; To – after thoracotomy and after 1-, 2-, 3-, 4-, and 5-minute periods of stabilization. *** $p < 0,001$ statistically significant differences between HRs measured during the light and dark part of the day.



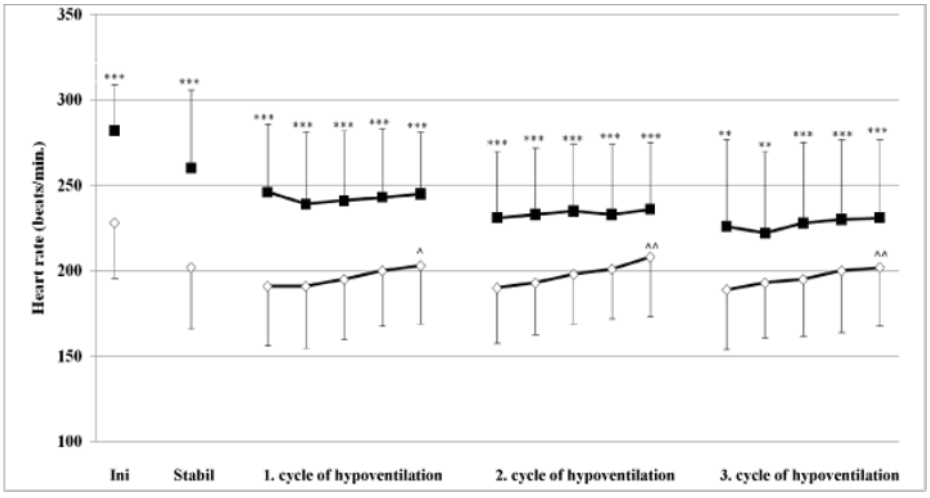
by one (n = 8 light, n = 9 dark), two (n = 10 light, n = 15 dark) and three (n = 8 light, n = 11 dark) 5-minute cycles of hypoventilation, each separated by 5-minute cycles of reoxygenation. During the experiment, all animals were subjected to 20 minutes of artificial hypoventilation-induced asphyxia (Scheme 2).

The animals were in the supine position on a pre-heated table; the trachea was exposed at the midcervical level and cannulated by a plastic tube. The tracheal cannula was attached to a volume-rate-regulated artificial ventilator (UGO BASILE), and the animals were ventilated with room air. The characteristics of the initial ventilation and reoxygenation were a respiratory rate of 50 breaths per minute and a tidal volume of 1 ml per 100 g of body weight (b.w.). During experimental hypoventilatory asphyxia, the respiratory rate and tidal volume were reduced to 20 breaths per minute and 0.5 ml per 100 g b.w., respectively. The respiratory effect of the ventilation was monitored by analysis of the blood gases and acid–base balance. The changes in the blood gases and acid–base balance were detected from blood samples taken from the arteria femoralis in intact, spontaneously breathing animals (light pH_a 7,326 ± 0,04, paO_2 6,05 ± 1,07 kPa, $paCO_2$ 8,23 ± 1,12 kPa, O_2 saturation 84,54 ± 3,06%; dark pH_a 7,295 ± 0,03, paO_2 7,17 ± 1,08 kPa, $paCO_2$ 7,16 ± 1,08 kPa, O_2 saturation 73,78 ± 12,3%), after 5 minutes of stabilization period, which followed surgical interventions (tracheotomy, thoracotomy) (light pH_a 7,362 ± 0,07, paO_2 8,25 ± 1,72 kPa, $paCO_2$ 6,03 ± 1,02 kPa, O_2 saturation 86,85 ± 8,59%; dark pH_a 7,531 ± 0,17, paO_2 8,15 ± 2,69 kPa, $paCO_2$ 3,83 ± 1,89 kPa, O_2 saturation 90,03 ± 9,41%), and at the end of 20 minutes of hypoventilation (light pH_a 7,136 ± 0,05, paO_2 6,76 ± 2,53 kPa, $paCO_2$ 7,57 ± 1,2 kPa, O_2 saturation 65,2 ± 15,42%; dark pH_a 7,16 ± 0,06, paO_2 7,31 ± 1,67 kPa, $paCO_2$ 7,2 ± 1,18 kPa, O_2 saturation 71,56 ± 12,3%).

The chest was opened by parasternal thoracotomy for the elimination of the nervous control mechanisms in breathing and for measurement of the threshold of ventricular arrhythmia. Bipolar electrodes were attached to the upper and lower limbs, which were used for heart-rate and electrocardiographic recording, and were further analysed with a computer system (ECG Practic Veterinary, Prague). The measurement of the HR (the mean value of the last 4 cycles) was performed in intact animals (Ini - before the surgical interventions in the supine position, spontaneously breathing), after tracheotomy (Tch) and thoracotomy (To), after each minute of 5 minutes of stabilization (Stabil - the parameters of the normal artificial ventilation), after each minute of preconditioning cycles by systemic asphyxia, and after each minute of 20 minutes of hypoventilation. Given that the animals from each group experienced the same conditions from the start of experiment, the HR was summed to one average value for intact animals, after the tracheotomy and thoracotomy, during the period of stabilization, and during the single cycles of asphyxic preconditioning.

Data are presented as the average values ± SD. Statistical levels $p < 0.05$ were considered significant by non-parametric tests (Kruskal-Wallis test). The data were averaged from the trials that were performed independently of seasons, because circannual variation can also occure in followed parameters.

Figure 2. The asphyxic average heart rate (HR) values ± SD during preconditioning in the light (empty rhombus) and in the dark (black square) part of the day. Ini – intact animals; Stabil – after stabilization. *** $p < 0,001$; ** $p < 0,01$ statistically significant differences between HRs measured during the light and dark part of the day. ^ $p < 0,05$; ^ ^ $p < 0,01$ statistically significant HR difference between the 1-minute and 5-minute cycles of asphyxia.



3. Results

3.1. LD- dependent differences in the heart rate during surgical preparation

The changes in the HR during different stages of preparation for surgery showed LD-dependence. The initial HR data measured in the intact, spontaneously breathing animals anaesthetized with ketamine/xylazine (Ini, Figure 1) treated during the light part of the day (LP) were significantly lower compared to those from the dark part of the day (DP) (M ± SD, 231 ± 28 vs. 264 ± 31 beats/min, $p < 0,001$). Similar LD-dependent differences in the averaged HR values were maintained after tracheotomy and thoracotomy (To; LP 168 ± 39 vs. DP 218 ± 57 beats/min. $p< 0,001$, Figure 1) and after the onset of artificial pulmonary ventilation (5 min. after the onset, LP vs. DP, 202 ± 34 vs. 262 ± 44 beats/min $p < 0.001$). Interestingly, whereas the HR values in DP-treated animals usually returned to near the initial values within 1 to 5 minutes of artificial ventilation (5 min, 262 ± 44 vs. Ini, 264 ± 31 beats/min,), similar recovery was not seen in LP-treated animals (5.min., 202 ± 34 beats/min. vs. Ini 231 ± 28 beats/min.) (Figure 1).

The statistically significant LD differences were found in each cycle of preconditioning by hypoventilation-induced systemic asphyxia (Figure 2). HR changes in each cycle of asphyxic preconditioning showed LD dependence. In the light period of the rat regimen day, the HR was significantly increased in the 5 minutes in each cycle compared to 1 minute (1. cycle 203 ± 36 vs. 191 ± 35 beats/min., $p < 0,05$; 2. cycle 208 ± 36 vs. 190 ± 32 beats/min., $p < 0,01$ and 3. cycle 202 ± 34 vs. 189 ± 35 beats/min., $p < 0,01$). In the dark period, the significant differences between 1 minute and 5 minutes of each cycle were not detected.

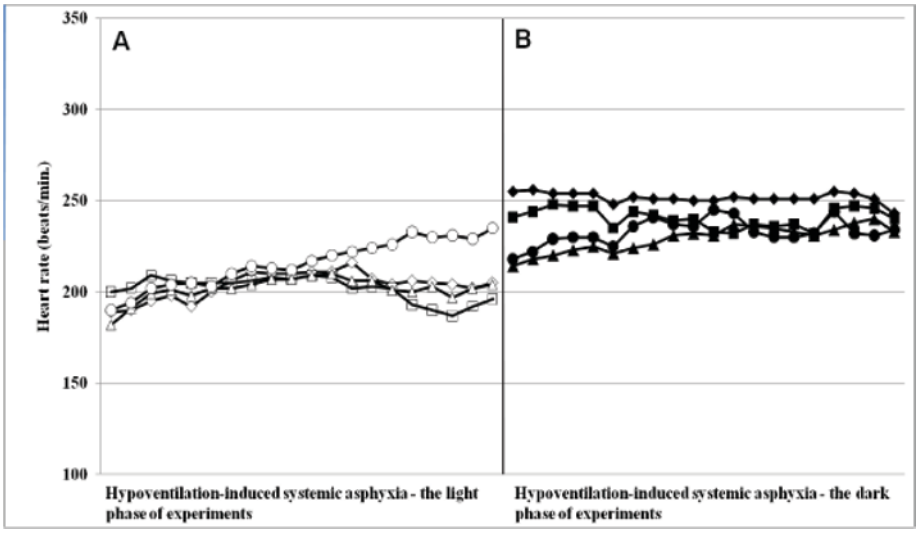
3.2. LD-dependent differences in the heart rate during hypoventilatory asphyxia

In the light part of the day, the HR increased gradually with the duration of hypoventilation until the 10-minute to 11–minute of 20-minute hypoventilation-induced asphyxia in all the experimental groups and with the subsequent stabilization in the control, 1 PC, and 2 PC groups to the end of asphyxic period. The next HR increase was seen only in the 3 PC group with the significantly higher values in the 20-minute of hypoventilation-induced asphyxia against the control, 1 PC, and 2 PC groups (3 PC vs. control, 235 ± 36 beats/min. vs. 215 ± 36 beats/min., $p < 0,05$; 3 PC vs. 1 PC, 235 ± 36 beats/min. vs. 196 ± 26 beats/min., $p < 0,01$ and 3 PC vs. 2 PC 235 ± 36 beats/min. vs. 209 ± 29 beats/min., $p < 0,002$). In the dark part of the day, the HR was stabilized during the course of the entire period of asphyxia in all experimental groups (Figure 3).

4. Discussion

Although the results clearly indicate that HR changes differ in LD dependence during asphyxic preconditioning, some limitations reduce the qualitative output. The first limitation is a relatively large variation in HR responses, which is a problem for in-vivo studies. An explanation may lie in the production of spontaneous, unpredictable alterations in the reactions of animals to ventilatory

Figure 3. The average heart rate (HR) values during hypoventilation-induced systemic asphyxia in the control group and in the groups pre-treated by a different number of preconditioning (PC) cycles in the light (empty symbols) and the dark (filled symbols) parts of the rat regimen day, respectively. Control group – rhombus; 1PC group – square; 2PC group – triangle; 3PC group – circle.



changes under anaesthesia or in the changed activities of hormonal and homeostatic reflexes in animals. The second limitation is that the animals were in systemic hypoxia from the start of the experiment to its end independent of the LD cycle.

The effects of LD cycle on the cardiovascular reactivity in vivo under ketamine/xylazine anaesthesia. The present study showed that the cardiovascular responses in ketamine/xylazine paralyzed rats show statistically significant dependence on the LD cycle. It affirms that LD-related differences are not merely transient or procedure-dependent. They are a systematic response in animals under ketamine/xylazine anaesthesia ensured by distinct neuro-humoral regulations in the light and dark parts of day.

Our results show that ketamine/xylazine anaesthesia may exert an effect on baseline cardiovascular responses, as demonstrated by a decrease in the HR during spontaneous breathing before surgical interventions, but the anaesthesia does not disturb the LD-dependence [30]. This type of anaesthesia modifies acrophase, mesor, and amplitude of the daily rhythms, but without loss of the daily rhythmicity [27,28]. The preservation of LD dependence in the HR after the surgical interventions in our experimental model does not affirm the assumption that surgery can have a more marked effect on LD dependence than the simple effect of the anaesthetic agent [28].

The effects of asphyxia on heart-rate responses. The spontaneously breathing rats under ketamine/xylazine anaesthesia were in an asphyxic condition independent of the LD cycle from the start of experiment in vivo [31]. Thus, the disruptive effect of hypoxia on the LD-dependent differences in the HR-response curve was not affirmed, as suggested by other authors [32-35]. One of the main conclusions from our study was that the HR was statistically significantly and systematically higher in the dark part of the regimen day than in the light part of the day, including under asphyxic conditions, even though the HR-response curves practically paralleled each other (Figure 1).

Interestingly, we found that this type of anaesthesia expressively increases parasympathetic tone and decreases sympathetic drive in the rats (Švorc, Jr., unpublished observations). Although the HR was on the level of bradycardia, the onset of asphyxia was regularly accompanied by a decrease in HR. Hypoxic bradycardia may be also explained by the reduction of tissue noradrenalin [35,36]. In contrast, in rats with moderate hypoxia, Ohkuwa et al. [37] observed an increased plasmatic noradrenaline level, serving as an indicator of increased sympathetic stimulation. The increase of the HR in rats was observed only after the first hour in the process of acclimatization, and then a decrease was found with amplitude reduction of the diurnal variation of the HR [38]. The relative contribution of afferent feedback, autonomic nervous drive, and direct hypoxic effect on circulatory responses was examined by Hayashida et al. [39] in conscious rats with or without chemoreceptor/baroreceptor input. Their data from hypercapneic hypoxia suggest that a CO_2–dependent chemical drive may contribute to a greater parasympathetic influence on the heart, similar to the asphyxia induced in our study. In addition to the differences in hypoxic protocols, afferent inputs, and behavioural state, sex-dependent differences may play

an additional role. Hinojosa-Laborde and Mifflin [40] reported the rise of HR after exposure to intermittent hypoxia in males but not in females, where the response could even be the reverse.

The effects of the LD cycle on heart-rate responses in conditions of preconditioning by systemic asphyxia. The light-dark adaptation has an important effect on the efficiency of the preconditioning mechanism in vivo as shown in our previous studies [26]. Our in vivo finding in the current study increases the practical value for pharmacological interventions, since the majority of the available data on myocardial ischemic or hypoxic preconditioning comes almost exclusively from in vitro studies [41,42]. Marked effects of the LD cycle on HR responses were not reported previously during defined stages of preparation for invasive surgery. In regard to the variability and effects of preconditioning by asphyxia, HR responses during the LD cycle obviously showed less pronounced dependence on the number of preconditioning cycles and exhibited less interindividual variability than in the dark part of the day, particularly during first half of the 20-minute hypoventilatory challenge. In the group adapted to the light part of the regimen day with 3 preconditiong cycles (Figure 3), the HR responses after 10 minutes of recovery lost obvious LD-dependence. This may suggest that, although preconditioning by 1 to 2 short cycles of asphyxia does not obviously alter LD-dependent differences in vegetative drive to the heart, several more cycles may eliminate the circadian effects. Alterations in the sensitivity of cardiac conductive system and local effects of hypoxia and acidosis on the myocardium remain unclear and require further elucidation, whether observed LD-dependent effects on asphyxia reflect the variations in the autonomic nervous inputs or represent more complex effects including the remodelling of the preconditioning mechanism,

This model does not offer a guide for treatment of serious ventricular arrhythmias. This model uses systemic asphyxia as preconditioning in order to produce a cardioprotective effect via autonomic nervous system activity. Synchronization of the patient to local time may be important for the evaluation of factors that increase or decrease the risk of cardiac rhythm disorders. Analysis of autonomic nervous system reactions (i.e., measured heart rate) to acute systemic asphyxia induced by hypoventilation is important to experimental cardiology, considering the fact that the autonomic nervous system reacts differently to systemic asphyxia in various day-times and is dependent on synchronization with external environmental periodicity.

Acknowledgments

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