Chapter 8

Ontogenetic Development of Neural and Muscular Rhythmic Activity and Its Regulation in Mammals during Perinatal Period

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Abstract

This review covers our recent advantages in studying the ontogenetic aspects of physiological mechanisms underlying regulation of rhythmic behavior. We have revealed that excitation patterns that emerged at early stages of phylogenetic development of life forms contribute greatly to the rhythmic activity of living vertebrates and invertebrates. These patterns govern spontaneous excitation, which is easily observed during the early stage of ontogenesis. The intensity and patterns of rhythmic activity are determined by nature and kinetics of certain metabolic reactions. During perinatal and sometimes postnatal periods (as in prematurely born animals), endogenic rhythmicity of developing physiological structures is strongly pronounced due to relatively stable living conditions. This rhythmic behavior is coordinated within an entire organism. Its integration in multiple systems is driven by amplitude and frequency modulation yielding rhythms of various frequency ranges. Indeed, it is the complex and conjoint functioning of physiological systems that maintains homeostasis in developing organisms. We present the results of our authentic research concerning the evolution and ontogeny of regulatory mechanisms of motor, cardiovascular, and respiratory systems. The aspects of intact and disrupted development are considered, involving the changes in dopaminergic, norepinephrinergic, and cholinergic system activation.

Keywords: evolution physiology, perinatal development, biorhythms, metabolism, neuropharmacology, heart rhythm, motor activity, respiration

1. Introduction

Endogenic rhythmic activity prevails during prenatal and—in immature animals—postnatal periods due to relatively stable living conditions. This rhythmic activity is strongly coordinated on an organism level. Its integration is done through amplitude and frequency modulation which yields rhythms of several frequency ranges. Only conjoint activity of all systems provides the main life-supporting factor—homeostasis of a developing organism.

The concept of archetypal "primary rhythms" was formulated by Voĭno-Yasenetskii A.V. as a result of long-term physiological research. Excitation rhythms detected in a complex organism or a cell located in a non-oscillating environment are considered primary rhythms. "Development of periodic nature of rhythmic excitation of cells is a result of subordinacy of biochemical processes kinetics to periodic impact of external environment during the early stages of life development" [1]. Primary rhythms are not exclusively attributable to primitive life forms or early developmental stages of living organisms. Complexes of periodic activity also persist in higher animals during the ontogenetic development and maturation of reticular systems, involved in synchronization of other brain structures. Considering the principles of CNS evolution during ontogenesis of vertebrates, Voĭno-Yasenetskii emphasized that it is the rhythm that serves a basis for CNS motor function development, and brain development in all warm-blooded animals follows the same principle of evolution [1].

We hold onto a classification of biorhythms, proposed by J. Salanki, who divided biological rhythms into three categories: micro, meso, and macrorhythms [2]. Rhythms which fall into a mesogroup and have a period between 1 s and several minutes are of the greatest interest for us. Excitable structures of organisms including Protozoa and higher animals produce primary rhythms which belong to this group. It should be noted that endogenic rhythms of various frequency ranges often coexist and are to be considered in a robust relationship.

The problem of endogenic rhythms origin is very complicated and is not resolved yet. We could not provide even a superficial review of available hypotheses and scientific data within the scope of this chapter. Therefore, we briefly discuss several publications concerning periodic nature of biochemical and biophysical processes. It was shown that glycolysis oscillation period falls into the 1–3-min interval; succinate oxidation has a period of 15 s, and ATPase rhythm has a period of 3–5 s [3–6]. Analysis of background oscillations of neuron cytoplasmic microstructures has revealed rhythms with periods of 1–2 s (movement and aggregation of mitochondria, chromatin pulsation) and 15–30 s (change of distance between axon hill and nuclear) [7]. The research carried out on isolated crawfish mechanoreceptors has helped register oxygen consumption oscillations with a period of 11–18 s, where amplitude increases dramatically on cell functional state change. Spectral analysis helped establish several groups of discrete periods of oscillations of mitochondria aggregations in various functional states of a neuron: 3–5, 11–18, 28–40 s, and 1–3 min. Time parameters of cellular energetics are probably associated with metabolic energy expenditure. "Superslow rhythmic oscillations of action potential," according to Aladzhalova N.A. terminology [8], or "slow electric processes," as defined by Ilyukhina V.A. [9], were found and extensively studied in cortex and deep

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structures of the brain in warm-blooded animals. These groups of potentials embraced rhythmic oscillations with periods between 2 s and 6 h. It was detected that sleep spindles in newborn rabbit cortex have a period of 10–15 s and coincide with motor activity [10]. Rhythms with period ranges considered in this chapter were classified by researchers into near-second (2–12 s), decasecond (15–20 s), near-minute rhythms (1 min) [8], or ζ-waves (2–10 s), τ-waves (12–60 s), ε-waves (1–5 min). Each range includes several subranges with varying physiological features [9].

Currently, there are no generally accepted time intervals for rhythm periods of given frequency ranges. Scientific data obtained in our research let us classify them into the following groups: near-second rhythms with a period of 0.5–3.5 s, decasecond rhythms (4.5–45 s), near-minute rhythms (50–120 s), and multiminute rhythms (125–600 s). This classification is not robust, because rhythm periods may vary greatly due to certain functional changes (periods sometimes shift quite considerably to an adjacent frequency range) [11]. We avoid contiguously defining the rhythm periods, because rhythm lability is an indispensable feature of an excitable structure.

2. Development of rhythmic functions during prenatal ontogenesis in rats

It is well established that endogenic rhythms of near-second and near-minute periods—the basis of spontaneous excitation—have relatively close origins, independent of the excitable structure or a functional system they belong to. Our data, backed by other researches, have shown that rhythms of the same frequency range detected in various functional systems of an organism are tightly adjacent by their ontogenetic dynamics and share regulatory, mediatory, and metabolic status on a certain developmental stage. Ontogenetic trends of rhythm timing parameters are most marked in near-second rhythms, which are detected in the gastrointestinal tract, motor, and respiratory activity. Rhythm period decreases soon after birth and up to postnatal day 16 (P16). For instance, a respiration rhythm decreases from 1.3 to 0.4 s and a locomotor rhythm—from 1.4 to 0.7 s. Later, gut rhythmic segmentation period declines from 3.5 to 2.2 s, probably due to changes in feeding behavior. Decasecond and near-minute rhythms do not undergo such dramatic changes, and their timing parameters do not alter over time. It is probably related to two aspects: (1) high rhythm variability is due to a wide frequency range and (2) such rhythms often have a modulating activity, that is, generated by early maturating structures [11, 12].

Spontaneous periodic motor activity is a dominant type of motor activity within prenatal and early postnatal periods of ontogenesis. Its periods are conventionally classified into near-second, decasecond, and near-minute periods (**Figure 1**). It was shown that heart, respiratory, and motor activities in rat fetuses with normal blood circulation change on embryonic days 15–20 (E15–20). Motor activity of rat fetuses has a complicated periodic pattern, resulting from three main types of locomotion. The first type corresponds to a generalized activity—body flexions and limb movement. Generalized activity peaks on E18 and completely

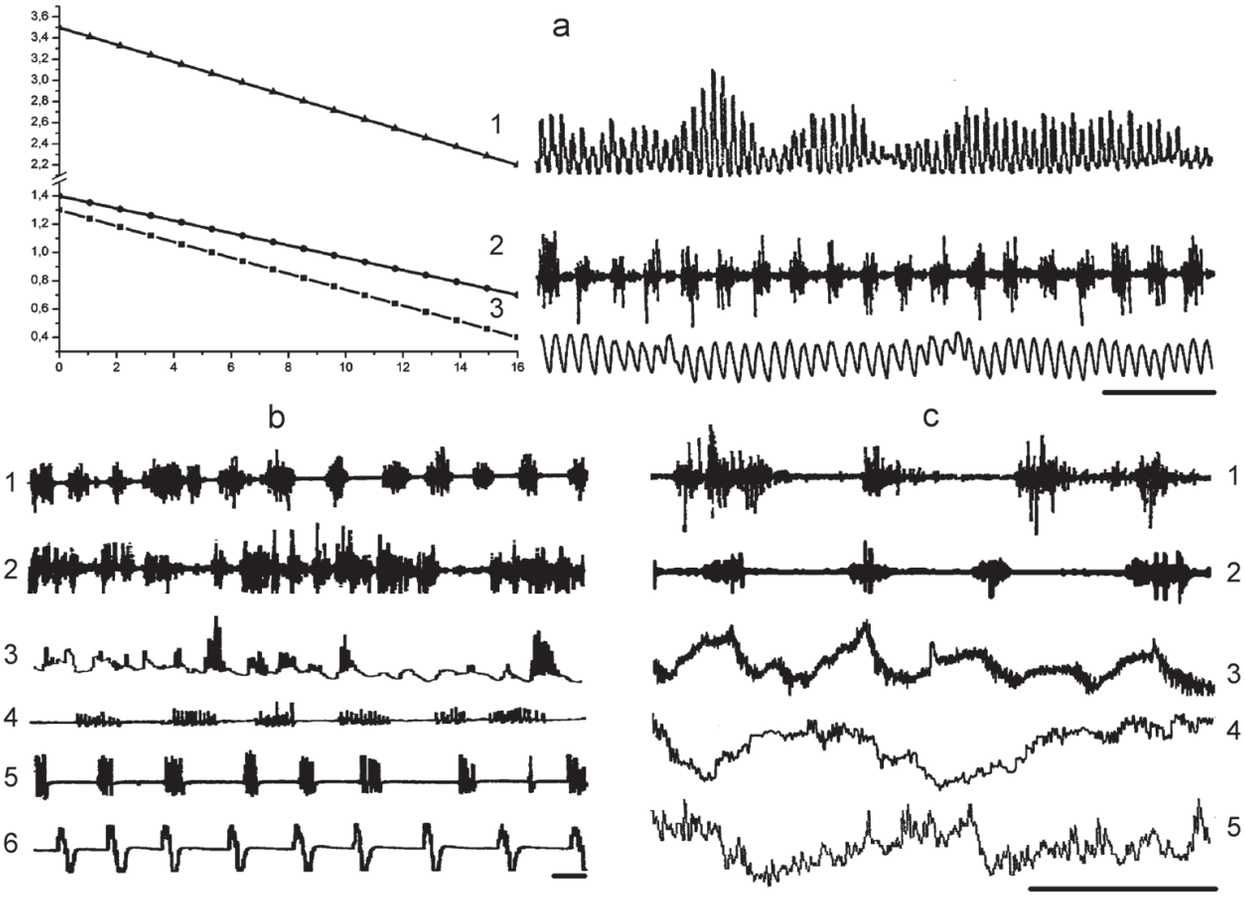

Figure 1. Examples of rhythms of various frequency ranges. Ontogenetic dynamics (a, on the left) of period of near-second rhythm and its reproduction (a, on the right) in pattern activity of gastrointestinal tract (1), SPMA (2), and respiration (3). Abscissa: Age of rat pups (days), ordinate: Period of rhythm (s). Time bar for electrograms: 10 s. (b) the appearance of decasecond periodicity present in SPMA of the 5-day-old rat pup (1), SPMA of the 2-day-old rat pup after administration of isoamine at a dose of 3 mg/kg (2), spontaneous contractions of isolated duodenum after addition to incubation solution of lysenyl at a concentration of 3×10^{-8} M (3), mechanogram of the 5-day-old rat pups after administration of hydrogen peroxide at a dose of 125 mg/kg (4), respiratory rhythm of 0-day rat pup after administration of lobeline at a dose of 50 mg/kg (5), respiration of adult human (6). (c) The appearance of the near-minute activity rhythm in SPMA of the 5- (1) and 10-day-old (2) rat pup, cardiointervalogram of the 5-day-old rat pup (3), spontaneous contractions of isolated ileum of the 30-day-old rat pup (4), and spontaneous contractions of isolated duodenum of adult rat (5). Time bar (s): (a), (b)—10, (c)—30.

disappears on E20. Burst duration increases initially from 17.1 ± 1.8 s on E16 to 36.7 ± 12.0 s on E18 and then decreases to 9.7 ± 1.0 s on E20. The second type of locomotion is related to local body movements which have a duration of about 5 s. They may produce series of 3–7 movements occurring in a decasecond range. The third type arises as short—about 300 ms—irregular extensor jerks. Local movements and jerks are typical of all ages, but they appear to be the main type of activity on E20. The development of respiratory activity sees a gradual transition from separate breaths on E16 to a series of breathing movements on E17–18 and then to episodes of periodic respiratory activity.

The analysis of interactions between respiratory and locomotor systems has shown that every breathing movement in 16-day fetuses is accompanied by an extensor jerk. Respiratory and locomotor activities are mostly uncoupled by E19. Heart rate increases from 175.9 ± 6.1 on

E15 to 271.8 ± 5.9 bpm on E20. Newborn rats have a volatile respiratory activity with considerable variations of rhythm and amplitude. Sometimes apnea periods are detected in rat puppies. Respiratory rhythm is strongly associated with other aspects of respiratory activity. Destabilization of respiratory rhythm accompanies not only complexes of motor activity but also single jerks. Respiratory rate variations which are related to SMA and observed at various ages have different trends. Rat puppies on P0-1 exhibit a tendency toward decreasing respiratory rate during rest (between complexes of locomotor activity), wherein a burst of locomotor activity is accompanied by acceleration of respiratory rate. SMA intensity declines by 2-week age; respiratory rate increases at rest and decreases during the burst of motor activity [13]. SMA which is detected in rat puppies during early postnatal ontogenesis consists of bursts of motor activity and rest periods. Activity-rest complex usually has a decasecond (40–45 s) or a near-minute rhythm. Decasecond rhythms can also be components of near-minute rhythms. Near-second rhythm as a basis of locomotor activity in mature animals is observed within bursts of motor activity with decasecond and near-minute rhythms. Near-minute rhythm of SMA is the most pronounced during early postnatal ontogenesis, while decasecond rhythm begins to prevail in the course of maturation. On acquiring a sense of sight and at the end of breastfeeding phase, periodic complexes of motor activity are replaced by near-second locomotor rhythm [14, 15].

Rhythmic activity of a certain frequency range can be simultaneously triggered by multiple physiological systems. Comparable rhythm parameters detected in many structures imply that there are common mechanisms of oscillation. The main candidate is a shared metabolic substrate. It is well known that evolution favors structures with slow oxidative phosphorylation, because it makes them less vulnerable to environmental changes. Phylogenetically oldest structures rely mostly on pentose phosphate cycle. They are able to retain automatic rhythmic functioning even in unfavorable conditions [16].

Our research has revealed that inhibitors of pentose phosphate pathway enhance the activity of physiological systems being studied. For instance, administration of hydroquinone to rat puppies completely eliminates rest from a typical activity-rest cycle of SMA, increases duration and amplitude of locomotor activity, and minimizes modulating rhythms [17]. Glucose is catabolized not only in pentose phosphate pathway but also mostly in glycolysis and citric acid cycle. Therefore, we carried out a research involving inhibitors of citric acid cycle. Newborn rats who were given sodium fluoroacetate intravenously died within a week: cachexia and developmental growth failure were observed. Heart and respiratory functions were not impaired in puppies unlike mature rats. This fact indicates that excitable structures are less dependent on aerobic metabolism at early ontogenesis. It is also supported by the absence of SMA arrest in test animals after administration of inhibitors. Citric acid cycle inhibition affects amplitude but not the pattern of SMA. The analysis of experimental and theoretical data suggests that cholinergic system plays a key role in physiological regulation when aerobic pathways are inhibited. Thus, a set of features specific to phylo- and ontogenetically early stages is manifested. Given that endogenic rhythmic activity is strongly tied with pentose phosphate cycle, we propose a hypothesis that citric acid cycle inhibition leads to redirecting carbohydrates to pentose cycle in excitable structures involved in excitation propagation [18].

Thus, we have established that glycolysis plays an important role in motor activity of newborn rats. Further research has revealed that bursts of SMA consisting of decasecond and near-minute rhythms are accompanied by a drop in serum glucose level. It should also be noted that activity pattern is affected by a feed state: emptying of stomach is followed by an arousal of decasecond rhythms and rapid jerks. Glucose level decreases by approximately 25% during rest and by 25–40% during activity. We have not detected any age- and pattern-related diversity. There is a seasonal variability in serum glucose level in newborn rats. However, there is a strong correlation between glucose level and motor activity pattern during all seasons except spring. The differences are smoothened in spring [19, 20].

Analysis of physiological parameters—heart and respiratory rate—in intact newborn rats has also shown a high correlation with season and feeding state. We also studied SMA parameters and blood glucose level in fed and fasting states (after a day-long starvation). Overall, blood glucose level in starved rats was 1.5–2.5 times lower than that in fed animals. Administration of glucose to fasting and—to a less extent—fed animals of all ages led to potentiation of near-minute rhythm of activity. Postnatal day 0 is an exception, as administration of glucose to fed animals intensifies decasecond rhythm and decreases overall motor activity. Blood glucose level and ontogenetic dynamics of SMA parameters in fasting rat puppies show a significant correlation that is not observed in fed animals: blood glucose level is higher during activity than at rest. Revealed ontogenetic variability of response toward glucose tolerance test is probably induced by morphofunctional maturation of locomotor system and carbohydrate metabolism juvenility. Our results suggest that intensity, duration, and pattern of SMA in newborn rats strongly depend on feeding state and can vastly change due to induced hypo- and hyperglycemia [21].

3. Development of cross-system interactions in perinatal ontogenesis of rats

The exact mechanisms of development and interactions of modulating rhythms remain unclear, but these problems are essential for ontogenetic physiology. It is well known that interactions between heart-vascular and respiratory systems are crucial for normal functioning of an organism. During prenatal ontogenesis, SMA plays a substantial role in morphogenesis and homeostasis. Functional activity of these systems has a rhythmic nature, and its coordination is crucial for homeostasis and adaptation to external and internal factors. In this section, we review some aspects of systemic interactions and regulation during late prenatal and early postnatal periods of ontogenesis.

We have obtained evidence that cardiorespiratory and viscerosomatic interactions emerge during prenatal period (E17–20) in rat fetuses. Tachycardia accompanied by R-R-intervals fluctuations develops during episodes of rhythmic respiratory activity. We have observed heart rate variability (HRV) in decasecond and near-minute ranges. Analysis of functional activity of cardiovascular and somatomotor systems has revealed that heart rate variability and burst of locomotor activity are independent. HRV becomes more synchronized with

motor activity during maturation. Short-term heart decelerations associated with motor activity are specific to E17–18. Their duration and amplitude are weakly dependent on locomotion intensity. Decelerations are superseded by acceleration reactions that are typical of a mature organism on E19–20. It is related to development of coordinating function of nervous system [22].

We have analyzed slow-wave oscillations of heart rhythm and motor activity in fetuses for any correlations with mother's heart rate in three frequency ranges: decasecond, D1–0.02–0.2 Hz; near-minute, D2–0.0083–0.02 Hz, and multiminute, D3–0.0017–0.0083 Hz. Pearson coefficient of correlation, its sign, and time shift have been estimated as correlation parameters. No correlation has been found in D1 range without regard to age. Correlations are higher in D2 and D3 ranges. Maximum correlation has been detected on E18–19, when motor activity peaks. Respiratory and cardiovascular systems of mother affect the variability of rhythmic processes in fetuses to a certain extent. Heart rates of mother and fetus strongly correlate with E17 and E20, when motor activity is at its breakpoint–rising and falling, respectively. In most cases, heart rate variability of mother outruns variability of fetus in D2 and D3 ranges. Specific mechanisms of heart rate synchronization between mother and fetus are not known yet. There are two hypotheses: (1) similar oscillators with close parameters in mother and fetus and (2) mother's rhythm affecting fetus directly [23].

An example of synchronizing slow-wave constituents of rhythmic activity of mentioned functional systems is given in **Figure 2**.

Interactions between physiological systems through slow-wave rhythms manifest themselves more completely during postnatal ontogenesis. Respiratory system in fetus changes dramatically after birth, interfering with other excitable structures. During first hours after birth, interactions between somatomotor and cardiovascular systems strengthen. Accelerations are typical of newborn rats, being greatly affected by intensity of motor burst. Interactions mediated by D2 and D3 rhythms are most pronounced in intact rat puppies: extent of cooperation goes down in the following pairs—somatomotor and cardiovascular systems, somatomotor and respiratory systems, respiratory and cardiovascular systems. Correlation decreases from D3 to D1 range, D3 having a highest correlation. D1 rhythms do not participate in intersystemic interactions. Changes in SMA intensity and pattern have a tendency to outrun modulating oscillations in D2 and D3 ranges of heart and respiratory rhythms [13, 24]. Consequently, systemic interactions in newborn rats are accomplished mostly by slow-wave oscillations of D2 and D3 ranges. Rhythms of decasecond range, D1, do not play an important role in integrative processes.

These mesorhythms were detected in fast temperature fluctuations in newborn rats up to 1 week of postnatal development. It was observed that body temperature fluctuated with an amplitude of 0.04–0.09°C, which corresponded to near-second and near-minute rhythm ranges. These temperature fluctuations coincide with rhythmic excitation in other functional systems. There is a clear correlation between bursts of SMA and temperature oscillations. Simultaneous recording of rectal temperature, respiratory rate, SMA, and electric activity of stomach established that temperature oscillations were more frequent than motor bursts or stomach activity. High-amplitude spiking activity of stomach muscles surpasses complexes

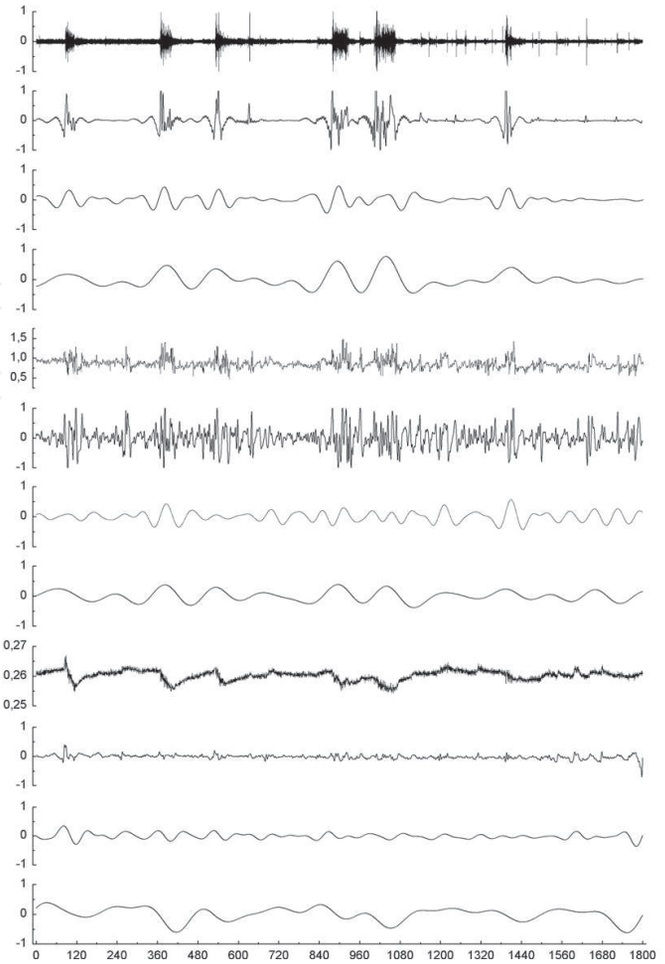

Figure 2. An example of production of initial signals. In (a)—EMG filtration (1), periodograms of the respiration rhythm (2), periodograms of the cardiac rhythm (3) to the slow-wave components (diapasons D1, D2, and D3). Abscissa: time (s), ordinate: the amplitudes of EMG signals, D1, D2, and D3 (stand. units); the periodograms of respiration and cardiac rhythms (s).

of motor activity and fits temperature peaks. Temperature fluctuations are unlikely to play a key role in thermal regulation due to low amplitude and high frequency. Most probably, these oscillations are mediated by systemic vasomotor reactions. Such temperature variations may indicate metabolic dynamics and may serve as a trigger to rhythmic excitation. They may also be involved in synchronization of rhythmic activity in various structures [25].

4. Monoaminergic regulation of rhythmic activity during perinatal ontogenesis in rats

Maintaining relevant rhythmic activity of physiological systems is essential for normal functioning and homeostasis. It is well known that rhythmic activity of visceral and somatic organs or systems of organs includes not only inner rhythms but also the activity of interacting structures (outer rhythms). Rhythmic activity integration is accomplished with its

amplitude and frequency modulation by rhythms of higher orders. Integration pattern is related to development of regulatory systems. It was shown that alterations in thresholds of cholinergic and adrenergic systems could result in severe functional disorders including cardiovascular and respiratory abnormalities [15].

Catecholaminergic system is notable for its early ontogenetic development. However, research carried out on fetuses is limited. This fact complicates analysis of underlying processes leading to dysfunction development in newborn animals. We have conducted a pioneering physiological research in rat fetuses (E17–20) and in newborn rats (P0–1) in vivo. Results included cardiovascular, respiratory, and somatomotor activity parameters in dynamics. The experiments were conducted in intact and test animals that were exposed to physiological and pharmacological activation of dopaminergic and noradrenergic systems [26–29].

L-DOPA was administered to animals to increase catecholamine levels in doses of 25, 50, and 100 mg/kg. The activation of catecholaminergic structures was induced by administration of isoamine (an indirect adrenergic agonist) in doses of 3 and 10 mg/kg. Moreover, we studied action of L-DOPA and isoamine after blockade of D1-receptors (by an antagonistic drug SCH-23390, 0.1 mg/kg) and D2-receptors (sulpiride, 50 mg/kg).

It was discovered that injection of L-DOPA resulted in continuous generalized motor activity in dose-independent (E17–18) and dose-dependent manner (E19–20). Respiratory rate in fetuses increases after L-DOPA injection. The number of fetal respiratory movements (gaspings) increases by 3–7 times. Heart rate is not affected considerably by L-DOPA. Our experiments that involved clonidine, an α-adrenergic agonist (1 mg/kg), administration to fetuses show that noradrenergic system of fetuses is capable of stimulating respiratory activity.

Novel head movements having a near-second rhythm appear between E18 and E19 during ontogenesis in 92% of fetuses. Mature activity patterns emerge in response to L-DOPA after E19: stereotypical head movements (circular movements, lateral and dorsoventral flexions) and alternating forelimb movements. Effects of L-DOPA derivatives—noradrenaline and dopamine—were brought into question. Based on theoretical and experimental data obtained by us and other authors, we expected L-DOPA to activate noradrenergic system. Stereotypical behavior in mature animals is currently associated with dopaminergic system by many authors. It seems well reasoned to suggest that dopaminergic system is also responsible for stereotypy in fetuses. We studied the effects of dopamine antagonists in fetuses on E19–20 and revealed that D1- and D2-receptor blockade did not affect motor activity of fetuses. L-DOPA induced the same effects when given with inhibitors. It implies that stereotypy in fetuses is not linked to dopamine system. Dopamine antagonists do not alter gasping and do not block L-DOPA effects on respiratory activity. DOPA can act as a CNS neurotransmitter binding to D2 and β2-adrenergic receptors [30]. We studied propranolol effects and came to conclusion that this phenomenon might be linked to noradrenergic system.

Endogenic monoamines triggered by isoamine tend to stimulate motor activity in fetuses on embryonic days 17–18. Isoamine induces two types of reactions on E19–20: a short activation of motor activity followed by inhibition (in 60% fetuses) and overall inhibition

(in 40% fetuses). It is likely that noradrenergic regulation is altered on E19–20 (before birth). Excessive concentration of catecholamines favors an increase of motor activity. Endogenic catecholamine release is followed by a short-term stimulation and then inhibition. Activation of catecholaminergic pathways leads to significant increase of motor activity during postnatal ontogenesis. Isoamine augments respiratory movements by two times on E17–18. We have observed an activation of respiratory activity in 60% fetuses and reduction in 40% fetuses on E19–20. Heart rate rises slightly on E17–18 and then decreases on E19–20. Heart rate and respiratory rate decrease slightly in newborn rats on administration of isoamine. D1- and D2-receptor blockade does not alter motor activity, respiratory, and heart rates of fetuses. Subsequent physiological or manual activation of catecholaminergic systems results in multiple reactions due to ontogenetic and individual features of animals.

Newborn rats are also subject to dose-dependent increase of SMA by L-DOPA. Stereotypical head movements (up-down, from side to side), body movements, and alternating limb movements are observed. Motor bursts occurring in a decasecond rhythm are significantly enhanced. Two-week rat puppies are also subject to increase of motor activity triggered by L-DOPA. However, this effect is less pronounced than in newborn rats. Locomotor rhythms are dominant in such motor activity.

Catecholaminergic system-induced respiration effects change remarkably on P0–1: excessive catecholamines release results in an increase of respiratory movements (gaspings) during prenatal period, and respiratory rhythm slows down on P0–1. Release of catecholamines potentiates SMA in newborn rats. D1-receptor blockade stimulates SMA. D2-receptor antagonists slightly augment SMA. L-DOPA further stimulates motor activity and changes its pattern. We detected oscillation complexes which had a period of about 3–6 min and tendency to expand and shift to a continuous mode. Motor complex patterns consist mostly of locomotor rhythms. Stereotypical movements are preserved. Isoamine injected after D2-receptor blockade had a weaker effect than that injected after L-DOPA administration.

Heart rhythm of intact newborn rats is a sinus rhythm with amplitude and frequency modulation. Single or multifocal extrasystoles are occasionally detected. Slow-wave modulation of heart rhythm in intact rat puppies consists of frequency oscillations falling into decasecond and near-minute ranges. These modulations are subdivided into asynchronous (mostly) and synchronous (with SMA complexes), the latter bearing a tachycardial pattern. Moreover, irregular bradycardial decelerations unrelated to motor activity are observed in heart rhythm. These fluctuations have a duration of about 10–30 s and an amplitude of 130–150% to a mean rhythm period of heart rate. D1-receptor blockade does not alter heart rate, while D2-blockade decreases heart rate. L-DOPA lowers respiratory rate when administered to newborn rats on P0–1. D1-receptor blockade does not change respiratory rate, but subsequent injection of L-DOPA leads to irregular respiration rhythm and low respiratory rate. D2-receptor blockade decreases respiratory rate, but this effect is opposed by L-DOPA. Stimulation of amplitude modulation is accompanied by an irregular respiratory rhythm.

We would like to draw attention to the data obtained during heart rate variability analysis. Spectrum power alterations in various frequency ranges were analyzed against physiological

parameters registered on administration of various drugs. It was revealed that newborn rats had unidirectional changes in spectra related to activity of catecholaminergic systems, while rat fetuses (E17–18) displayed a large variability due to the influence of multiple regulatory systems. During prenatal period, L-DOPA enhances neural regulation of vagosympathetic balance in 50% rat fetuses, which is caused by alterations in humoral and metabolic factors. In the rest 50% fetuses spectrum power is shifted toward slow-wave activity. Moreover, in 75% newborn rats, L-DOPA enhances high-frequency constituents of spectra, that is, humoral and metabolic influence is minimized. The observed changes involved activation of both sympathetic and parasympathetic systems. But parasympathetic effects are more pronounced, which is reflected by LF/HF coefficient means. Isoamine boosts sympathetic effects by 70–75%. It was revealed that neural regulatory mechanisms began to play a more important role in the regulation of heart rhythm in newborn rats. Sympathetic effects were observed in 60% animals. However, vagosympathetic balance shifts toward parasympathetic effects due to their prevalence in overall spectra.

So, it is known that D1 and D2 receptors are subject to heterochrony (in terms of physiological development). Earlier it was proposed that D1 receptors are physiologically inhibited within 30 days of postnatal ontogenesis [31]. This fact is backed by another research [32, 33]. But herein we show that D1- and D2-receptor blockade affects respiratory activity greatly on E17. Moreover, there are differences in the response to dopamine receptors antagonists in fetuses on E17–18 and E19–20. Similar results were obtained earlier as a result of motor activity analysis in fetuses on E21 with D1- and D2-receptor antagonists [33]. Based on our results, we suggest that catecholaminergic systems undergo significant changes during prenatal ontogenesis (E18–19). It is supported by the fact that an increase of catecholamines on E19 is accompanied by appearance of stereotypical movements, which is not inhibited by dopamine receptors and β2-adrenoreceptor blockade.

Thus, we have shown that effects of catecholaminergic and dopaminergic systems on heart and respiratory regulation change dramatically after the birth. Catecholaminergic system changes are the most pronounced. Respiratory system response to physiological and excessive concentrations of endogenic monoamines alters within a few hours in newborn rats. The variability of observed response depends on several factors: age, feeding state, and season. The significance of two latter ones was demonstrated in our recent work involving complex biochemical and physiological methods [19]. The key role of functional changes occurring in respiratory system and catecholaminergic structures activation is supported by our research dedicated to systemic interactions and reviewed in Section 3.

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