Plasticity of the Brain in Neuroontogenesis

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Abstract: Plasticity is a specific endowment of the nervous system to develop, to react or to adjust to the internal and external environmental changes, both in the physiological and pathological conditions. Cumulative evidence has revealed the dynamism of the nervous system, based on the balance between the rigidity and plasticity. Different aspects of neuroplasticity can employ common general cellular mechanism. Effects of plasticity can be either positive or negative changes during the development (evolutional plasticity), after the short-term exposition (reactive plasticity), after the long-term or permanent stimuli (adaptational plasticity), and during functional or structural recovery of the damaged neuronal circuits (reparation plasticity). Manifestations of plasticity have probably the same basis, irrespective of a cause, which triggered them, or the brain region where they were accomplished. Activity of neuroplastic processes appears to be especially high in the immature nervous tissue.

Key words: Neuroplasticity – Evolutional plasticity – Reactive plasticity – Adaptational plasticity – Reparation plasticity – Critical periods.

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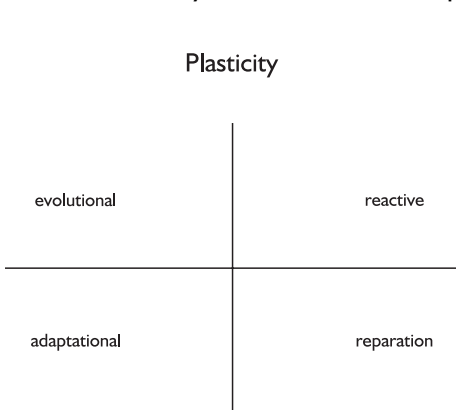
Nervous system is not only able to respond to new stimuli but it is able to adjust its responds. Such changes can develop only in conditions of versatile and adaptable interaction among the individual regions of the nervous system. Functional changes represent modifications of the system, which accomplishes them. Changes are possible only in conditions of certain compliance or plasticity of the nervous tissue. It shows that all the forms of plasticity both at the level of individual neurons, level of activity of the entire nervous system and the level of behaviour are based on changes on a molecular level. Such changes, as well as changes at the systemic level are expressed in actual adjustments of the structure, biochemical or functional processes, both in the time and space. Immature cells have their further development genetically predetermined [1]. Their limited functions, immature structure and non-finished metabolic development [2, 3], is responsible for the structural development (e.g. myelogenesis, building up of functional membranes, ion channel maturation, production of neurotransmitters). A mature cell has all the given parameters stable and fully functional with high energetic requirements. However, such stability represents also a specific rigidity. Changes then are represented namely by a set of regulatory mechanisms of neurohumoral origin (reaction and adaptation). Most of that is not available in an immature cell. It is necessary to assume a mechanism, which can the undifferentiated neuron to form, adjust and to comply.

Definition of plasticity
Plasticity is a specific endowment of the nervous system to develop, to react or to adjust to the internal and external environmental changes, both in the physiological and pathological conditions. [4].

Elementary features of plasticity
Experimental findings and clinical observations have revealed the dynamism of the nervous system, based on the balance between the rigidity and plasticity. Plasticity of the neuronal system is based on comprehensive mechanisms, which have two characteristic manifestations: first type of the "functional" plasticity shows comparatively fast and results and reversible changes. The second type of plasticity has the form of adaptation and is based on the expression of genotype into phenotype [5].

Plasticity

evolutional   reactive

adaptational   reparation

Fig. 1 – Types of plasticity

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Classification of neuroplasticity

Effects of activation of neuroplastic mechanisms by various stimuli of the external or internal environment with different intensity and duration in different periods of life can be classified as the evolutional plasticity (during the development), reactive (after a transient exposition), adaptation (result from the long-term or repeated exposition) and reparation plasticity (functional or structural recovery of the impaired neuronal circuits – fig. 1).

Evolutional plasticity

Physiological development of organization of neuronal circuits and the onset of their function are controlled by genetic programs in cooperation with factors of the external and internal environment. Process of organization has three phases. During the first phase the future neurons proliferate, in the second they migrate to the place of their destination, and only in the third phase – during the differentiation – they assume the final size, length of processes and organization of their input and output circuits. These three developmental phases may overlap: the differentiation usually starts already during the migration, the proliferation may proceed also during the phase when part of the neuronal population already differentiates. The period of proliferation may differ for different cell types. Periods of macroneuronal proliferation (the principal neurons of the given population – e.g., the pyramidal cells in the hippocampus), microneuronal proliferation (interneurons or the neurons of the local circuits), and the period of glial proliferation can be distinguished. Similarly, the third phase of the differentiation can be divided. According to the classical description, the macroneuronal differentiation brings formation of the afferent and efferent pathways of the given functional system – the long connections are formed (coarse wiring). However, it shows that macroneurones may also send collaterals of their axons into the local circuits (Fig. 2); for example axon collaterals of the hippocampal CA_1 pyramidal neurons terminate at interneurons of the same
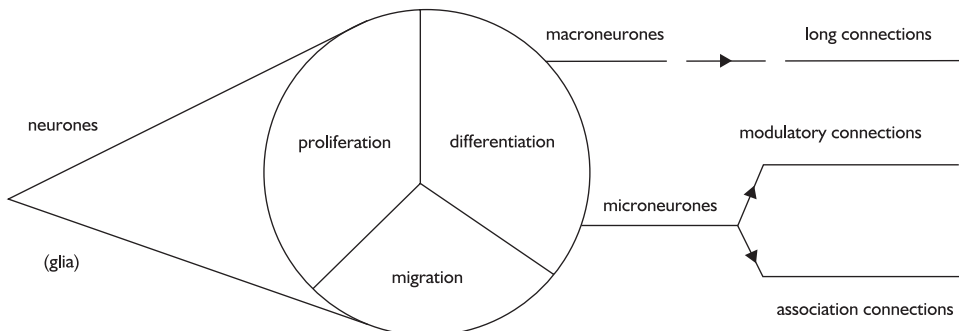
Fig. 2 – Developmental processes with neuroplastic contribution

region (Fig. 3). During the microneuronal differentiation, the association and modulation circuits are formed (fine wiring) (Fig. 2.). There are also some exceptions of this rule: some small neurons contribute not only to the local circuits but they send their fibers to the comparatively distant brain regions. The glial differentiation brings about the stability of the microenvironment of the neural tissue, communication with capillaries [6] and the myelin formation (fixation).

Developmental steps
Development and differentiation advances in successive steps. Development of the visual cortex and genesis of eye dominance may serve as an illustration. Visual deprivation or restriction of visual stimuli, e.g., by a unilateral eyelids stitch in newborn kittens results in a decrease of effectivity of the signal transmission at the side of deprivation. Activation effect of signals from the deprived eye on the neurons of the visual cortex became much smaller than that from the stimulated eye [7]. Majority of the visual cortex neurones favoured signals from the unrestricted eye (dominant position of the eye). Mechanism of the eye dominance development stands on the Ca^{2+} intracellular concentration changes
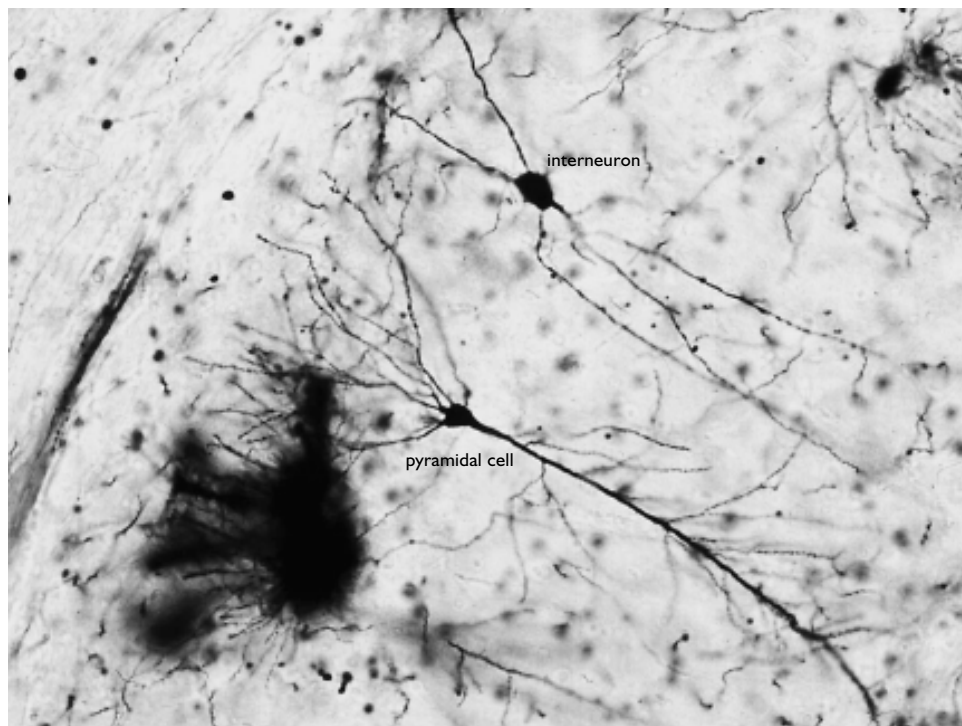

Fig. 3a – Pyramidal neurone (left) and interneurone (right) in CA$_1$ area of the hippocampus in the rat brain. Golgi impregnation (modification by Molinere)

(an increase in the stimulated neurones), which is related to the activation of NMDA receptors. Beside glutamate, also other neurotransmitters (norepinephrine, acetylcholine and GABA) may play an important role in the organization of neuronal networks [8].

Critical periods

Comparatively short period of the developmental progress, traditionally called *critical developmental period*, is usually accompanied by an increase of sensitivity to both positive and negative stimuli. The most vulnerable is assumed to be the period of the rapid growth [9, 10]. Vulnerability is probably not directly related to the speed of growth, it is more associated with differentiation (plasticity) of the sensitive structures and processes in the growing and therefore organising systems [11]. During the critical developmental period the organising process (morphogenetic function – [12] assumes the threshold level and specific stimuli of the external or internal environment, a well as an inadequate activity, may permanently alter the newly formed structure [13, 14, 15].

   Recent findings have brought deeper understanding of this process and revealed its cellular basis: Efficient stimuli may trigger or block the expression of genetic programs for the given structure or function. Outcomes of such activity become usually stable and the structure is losing sensitivity to formerly effective specific stimuli (qualitative changes of the neuroplastic potential). Changes accomplished in the period of organization are therefore long-termed or permanent. Functional modifications need not be immediate; they can turn out later as a result of some next developmental process. E.g., rats weaned prematurely (at PD 15) exhibited after sexual maturation an increased salt intake. The interference with organization process may have a wide spectrum of functional consequences: from an
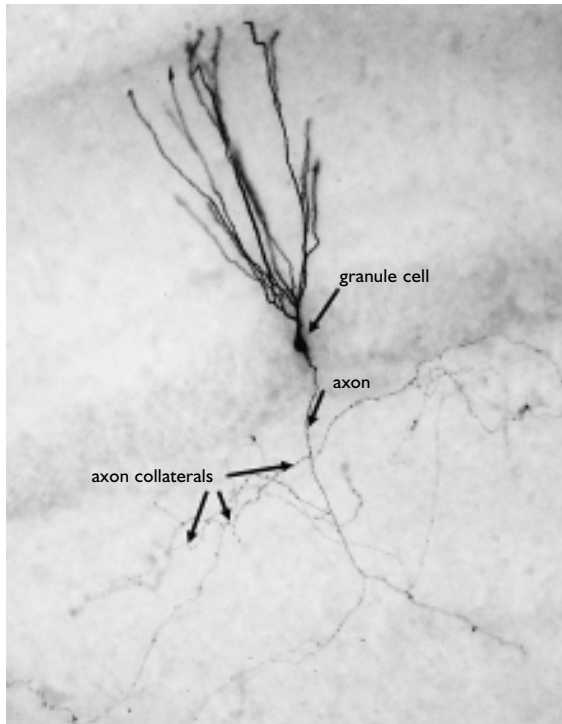

Fig. 3b – Granule cell with axon and axon collaterals (intracellular staining with Neurobiotine)

alteration (e.g. changes resulting from malnutrition or hypothyroidism) to mostly positive effects (stimulation or rearing in a complex environment during the development). A combination of several factors may thus limit effects of some negative stimuli (e.g., malnutrition can be partly compensated by a suitable sensory stimulation – [16], or by rearing the young animals in an adequate social environment) – [17].

Reactive neuroplasticity
One of possible tissue reactions to the environmental changes is an immediate response, which is limited to the period overlapping the stimulus exposition. We have described that various stimuli (brief period of starvation and thirst, impairment of some CNS regions, nociceptive stimuli, parenteral administration of water) increase resistance of the rat brain to the lack of oxygen, especially in the immature animals [18]. Immature nervous tissue has the capability to respond to changes in the internal environment by adjusting its metabolism at the cellular level. This process has been called adaptive metabolic reaction as it has both some features of a reaction and that of adaptation. It includes:

- increased utilization of endogenous glycogen, which is energetically more effective then utilization of free glucose
- a shift of cell oxidation towards anaerobic glycolysis with preservation of energetic sources (ATP, ADP, KP)
- increased activity of some enzymes, namely those participating on the anaerobic glycolysis
- preservation of the relation between aminoacid and glucose metabolism (Tab. 1).

If we remove for example, glucose from an immature neuron, it can utilize lactate or acetoacetate equally well [19]. In certain extent, it can modulate its energetical input. It is also possible that immature neuron can respond to a lower supply with oxygen not only by a decrease of its energy consumption [20], but can also increase the effectivity of oxidative phosphorylation [21]. The higher effectivity of oxidative phosphorylation probably results from the increased activity of oxidation enzymes with the key task of adjustments being the preservation of proteosynthesis. It can keep on building up the enzymatic capacity of immature neurons with a distinct compensatory character [18]. When pH of internal environment decreases, the immature structure and metabolism of neurons exhibit a higher resistance and therefore higher compliance to acidic environment enabling to survive [22]. Brain centres can be optimally interconnected only in the presence of physiological stimuli (visual, auditory, tactile etc.). At the same time they possess a reserve for the recovery of impaired connections by formation of new ones (based on possible plasticity). Impairment of the brain (e.g. by ischemia) during the delivery can be "compensated" by adequate therapy, which

means that such therapy can help to accomplish reparative (recuperative) processes based on neuroplastic mechanisms [23].

Possibility to activate neuroplastic mechanisms by influencing neuronal structure depends on the type of impairment and options to respond. A single factor may therefore have different effects during the intrauterine life, after the birth, during the weaning period, and in adulthood. At the same time, the sensitivity of individual systems plays also an important role [9, 10]. Powerful effect has a brief period of proteosynthesis arrest (e.g., by administration of cycloheximide – [24]. On the contrary, an increased stimulation in the early development often has opposite effects to those resulting from some forms of deprivation. Similar effects also have modifications of the social milieu [25].

Table 1 – Reactive and adaptive plasticity

Age		Reaction	Adaptive reaction	Adaptation
Level of the brain development		Mainly the immature tissue	Immature tissue	Mature and immature tissue
Effect (stressful stimulus)	– influence	single	single	long-term or successive
	– duration	short-term	comparatively short-term	always long-term
	– intensity	low medium high	low mainly medium	medium high
Response		local immediate	local immediate	systemic with latency, long-term
		mainly functional	mainly metabolic	both functional and structural

Table 2 – Adaptive plasticity

Local		General
Functional	Structural	
transmitter release	synaptic invagination	afferent and efferent input reorganization
action of receptors	spines and dendrites – shape and length	
intracellular mechanism of signal transmission	synaptogenesis	functional compensatory changes

Adaptational neuroplasticity

Can be elicited by a long-term or repeating stimulus. For example the long-term potentiation of the synaptic transmission in hippocampus (long-term potentiation – LTP) has several functional manifestations implicating changes of parameters of the transmission (Tab. 3 and 4). They may bring about an increase of the transmitter release or increase in the density of postsynaptic receptors for transmitters. Long-term potentiation has at the same time also its distinct structural component [26, 27]. Though LTP does not bring about changes in the density of synaptic vesicles, the number of presynaptic invaginations increases, which indicates a long-lasting increase of turnover of synaptic vesicles [28]. These findings support the view that the transmission changes are related to activation of the protein synthesis in the participating neurones. Proteosynthesis brings stabilisation of structural and biochemical transformations, induced by adaptation. For example the repeated lack of oxygen during repeated ischemia (totally 7 hours, 42 minutes) brings about no significant difference in the higher nervous functions both in the developing animals and in adults (Fig. 4, 5 a, b).

Table 3 – Reparation plasticity

Genetic program	
Functional	Structural
efficiency of synapses	number of synapses
modulation of local circuits	new fiber collaterals
interrelations among functional units	reorganization of local circuits

Table 4 – Summary of neuroplastic changes

Level synapses		Level of local circuits	Multimodulatory level
Functional (learning)	Structural		
dynamics of the mediator release	volume of the presynaptic zone	reactive synaptogenesis	plastic changes at the level of synapses and local circuits
receptor sensitivity	length of the active zone	remodeling of the dendritic tree	
activation of postsynaptic mechanism	number and distribution of vesicles	aberrant plasticity (recurrent inhibition)	ability of "tuning"

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Long-term and complex stimuli activate neuroplastic mechanisms not only at the level of synapses, but also at the multimodular level (Tab. 2). Altered shape and length of the dendritic branches may result in reorganization of the whole dendritic tree and consequently lead to the reorganization of afferent inputs.

Every adaptation represents a definite loss; whatever it is the matter, the energy or the information. Precisely that enables to observe a very significant phenomenon: during repetition of competent stimuli, living organisms are able to minimise such loss. It is true also for the neuroplasticity. Repetition is probably a source of experience, which the brain evaluates and subsequently minimizes expenses for adaptation. Such feature depends on age, developmental stage of organism and the character of adaptation stimuli (Tab. 1). Adaptation reaction comes from the level of neuronal membranes till intrinsic systems of the brain. They include both the temporary functional compensation (e.g. excitability changes of the immature brain after the single exposition to the altitude hypoxia – [29], Fig. 6) and the permanent reorganization.
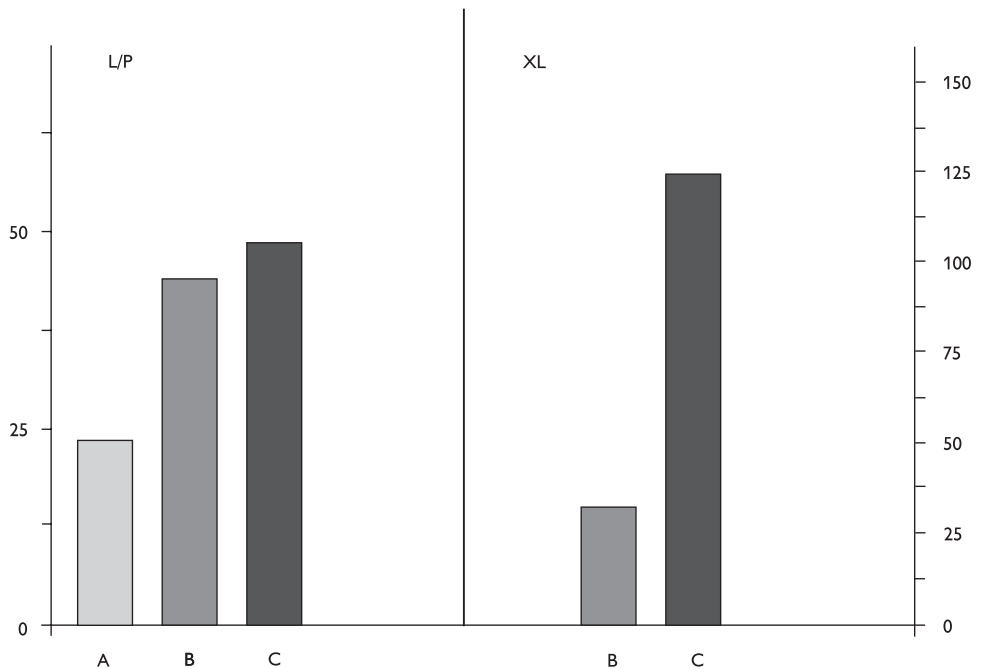

Fig. 4 – Lactate/pyruvate ratio (L/P) and excess lactate (XL) in prosencephalon of 18-day-old rats. Abscissa – A – L/P in controls, B – L/P and XL in rats exposed 1 min less than the lethal dose time to 10 G acceleration, C – L/P and XL in rats adapted to repeated exposure to 10 g acceleration twice a day, with a 4-hour interval, from birth to the age of 17 days. Ordinate – values of activity in arbitrary units

Reparation neuroplasticity
According to the accepted definition, one of the manifestations of neuroplasticity is the ability of the nervous tissue to recover its function disordered by an intervention into the organization. As the other discussed forms of plasticity, mechanisms of recovery are controlled by genetic programs, which determine activity of individual neural elements. These programs are triggered by changes in the internal environment of the nervous tissue, which accompany the pathologic process. Reparation may result from changes in the efficiency or in the number of synapses, from the rearrangement or from sprouting of dendritic and axonal branches [30, 31]. Reparation is accompanied by a reorganization of local neuronal circuits, or by changes in the relation among functional brain units (Tab. 3). Research is therefore currently searching a method how to reinforce the neuroplastic mechanisms (Tab. 4) and thus the regenerative capacity
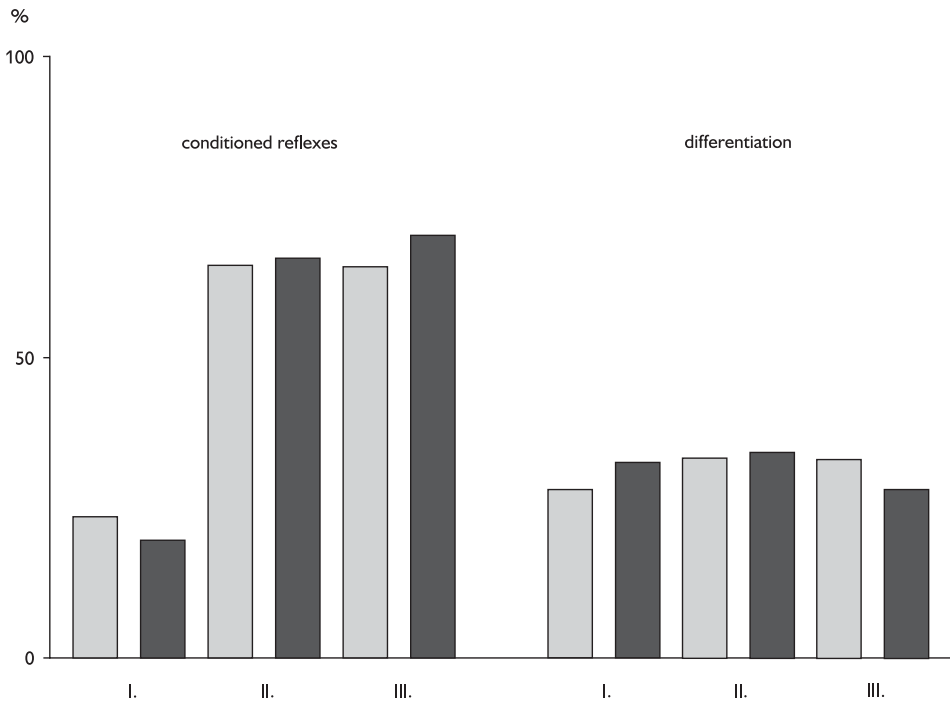

Fig. 5a – Elaboration of conditioned reflexes and differentiation by 21-day-old rats repeatedly exposed to 10 G acceleration twice a day, with 4-hour interval.
Abscissa: weeks of experiments
Ordinate: percentage of positive responses
Grey columns – experimental rats
Black columns – controls

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of the nervous system. By means of activation of the natural mechanisms or by an aimed medication, the intrinsic neuroplastic mechanisms may be activated, the "sleeping" process of regeneration may become working and it may bring up the recovery of injured neuronal circuits [4, 32].

The theoretical feature of nervous tissue plasticity brings about several questions: How to employ neuroplasticity in the clinical praxis? How to respond to the risk of perinatal brain impairment and its possible effects, namely the risks of mental diseases? Is it possible to stimulate plastic processes, which are assumed to be genuine features of the immature nerve tissue? Can be plasticity of a larger extent than we expect? What is the basis of plasticity – is it bound to something (structurally of metabolically) – or it represents only an existential possibility of the undifferentiated nerve cells? Is there any analogy to stem cells?
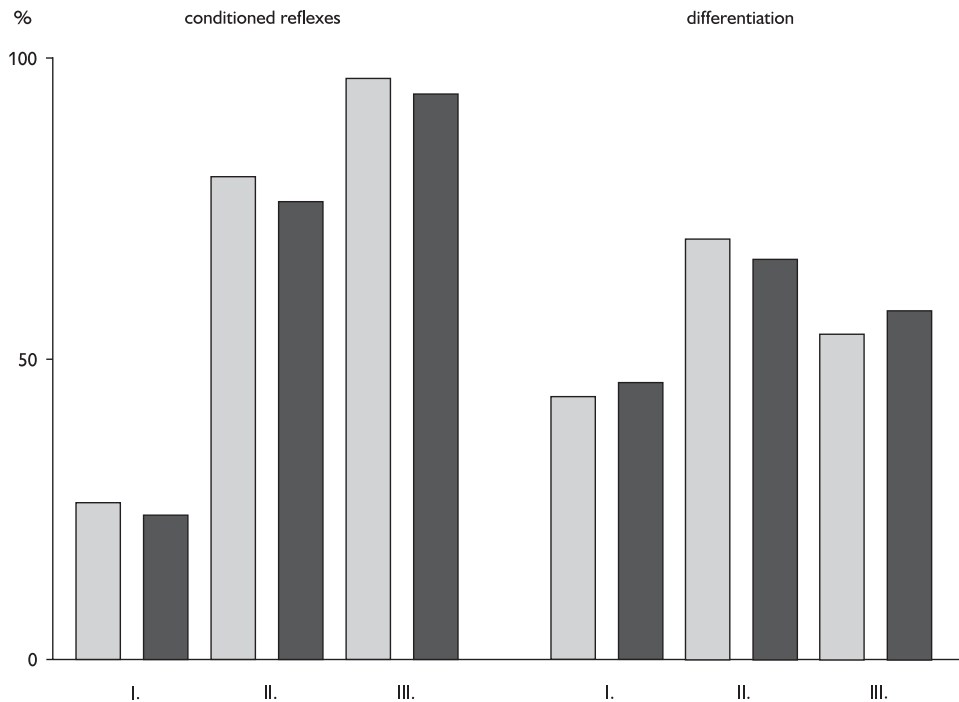

Fig. 5b – Elaboration of conditioned reflexes and differentiation by adult rats repeatedly exposed to 10 G acceleration twice a day, with 4-hour interval.
Abscissa: weeks of experiments
Ordinate: percentage of positive responses
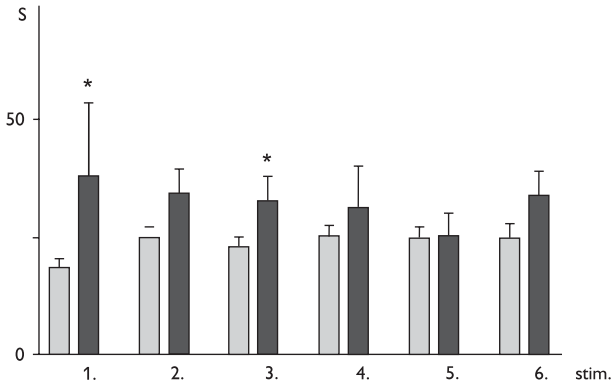Grey columns – experimental rats
Black columns – controls

Fig. 6a – Duration of evoked cortical afterdischarges in 12-day-old rats after repeated stimulation of the sensorimotor cortex
Grey columns – rats not exposed to hypoxia
Black columns – rats exposed to 1 hour hypobaric hypoxia on simulated altitude of 7000 m
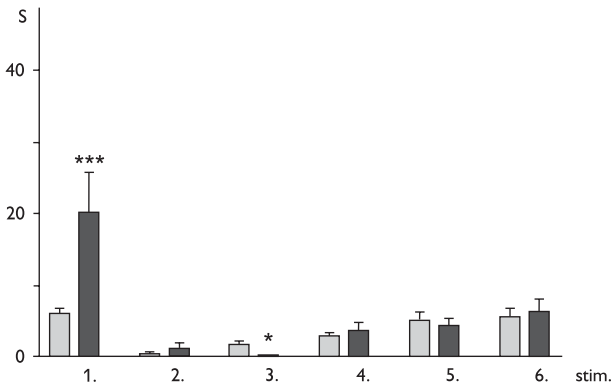

Fig. 6b – Duration of evoked cortical afterdischarges in 25-day-old rats after repeated stimulation of the sensorimotor cortex
Grey columns – rats not exposed to hypoxia
Black columns – rats exposed to 1 hour hypobaric hypoxia on simulated altitude of 7000 m
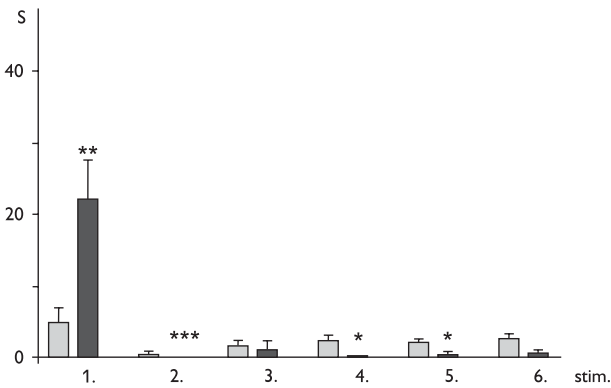

Fig. 6c – Duration of evoked cortical afterdischarges in 35-day-old rats after repeated stimulation of the sensorimotor cortex
Grey columns – rats not exposed to hypoxia
Black columns – rats exposed to 1 hour hypobaric hypoxia on simulated altitude of 7000 m

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Can the "deviated" plasticity explain the defective brain development or some of its functions? Is it therefore possible to assume plasticity as a positive feature (ability to compensate, replace, complete) or it has also negative effects?

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