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MINIREVIEW

Theoretical Aspects of Neuroplasticity

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Summary

The authors propose an integrative theory of the organization of neuroplastic processes. Neuroplasticity is assumed to be one of the essential characteristics of the nervous tissue which may be manifested comparatively rapidly and result in reversible changes (functional plasticity). It may also modulate the expression of genotype into phenotype (adaptation) and thus bring about long-lasting effects. Neuroplastic mechanisms are triggered by various natural or artificial stimuli, which may arise in the internal or external environment, and they may differ quantitatively or qualitatively. The effects of plasticity can lead to either positive or negative changes during development (evolutionary plasticity), after short-term exposition (reactive plasticity), after long-term or continuous stimuli (adaptational plasticity), and during functional or structural recovery of damaged neuronal circuits (reparation plasticity). Manifestations of plasticity have probably the same basis, irrespective of the cause which triggered them or the brain region where they were accomplished. Neuroplastic mechanisms are based on the modulation of signal transmission across synapses. They can be related to interneuronal relations. The resulting changes may occur in the communication between neurons (synaptic level), in the activity of local neuronal circuits (at the level of local circuits) or in the relations between individual functional brain systems (multimodular level).

Key words

Plasticity • Nervous tissue • Development • Adaptation • Reparation

Introduction

Plasticity is the specific endowment of the nervous system to develop, to react or to adjust to the internal and external environmental changes, both under physiological and pathological conditions. Scientific literature proposes various classifications and terminology in this field. The present authors therefore propose a unifying theory for explaining the organization of neuroplastic processes.

Experimental findings and clinical observations have revealed the dynamism of the nervous system, based on the balance between rigidity and plasticity. The plasticity of the nervous system is based on comprehensive mechanisms which have two characteristic aspects: the first type of „functional" plasticity is manifested comparatively rapidly and results in reversible changes. The second type of plasticity has the form of adaptation and is based on the transformation of genotype into phenotype. Methods of activating the neuroplastic mechanisms might become the most natural way of assisting the impaired brain.

Plasticity may cause both positive and negative effects during development (evolutionary plasticity), it

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may become evident after a transient exposition to a biologically significant stimulus (reactive plasticity), it may result from long-term or repeated exposition to such stimuli (adaptation plasticity), or it may participate in functional or structural recovery of the impaired neuronal circuits (reparation plasticity) (Table 1).

Table 1. Division of types of neuroplasticity on the basis of the recuperation potential of neurons

CLASSIFICATION OF NEUROPLASTICITY		
Effects		Manifestations
advantageous adverse	during development	evolutionary plasticity
short-term single	exposition	reactive plasticity
long-term successive	exposition	adaptive plasticity
functional structural	recovery	reparation plasticity

Evolutionary plasticity

The development of individual CNS regions is controlled by different morphogenetic systems, i.e. by sets of cell populations which carry, mold and accomplish programs for the formation of a given part of the brain. The organization of the neuronal systems and the onset of their function is governed by genetic programs in close cooperation with factors of the internal and external environment.

Table 2. Manifestations of plasticity during the maturation of neurons (glia)

EVOLUTIONARY PLASTICITY			
proliferation migration differentiation	neurons (glia)	macroneurons microneurons	long-distance connections association connections modulation

The organization of neuronal circuits has three phases (Table 2). During the first phase, future neurons proliferate, in the second they migrate to the place of their destination, and only in the third phase – during differentiation – they assume their final size, length of processes and organization of their input and output circuits. These three developmental phases may overlap: the differentiation usually already starts already during migration, the proliferation may also proceed during the phase when a part of the neuronal population is already differentiating. The period of proliferation may differ for different cell types. Periods of macroneuronal proliferation (the principal neurons of a given population, e.g. pyramidal cells in the hippocampus),

microneuronal proliferation (interneurons or neurons in local circuits) and the period of glial proliferation can be distinguished. Similarly, the third phase of differentiation can be subdivided. According to the classical description, macroneuronal differentiation brings about the formation of afferent and efferent pathways of a given functional system – the long connections are formed (coarse wiring). However, it shows that macroneurons may also send collaterals of their axons into the local circuits; for example, axon collaterals of the hippocampal CA1 pyramidal neurons terminate at interneurons of the same region. During microneuronal differentiation, association and modulation circuits are formed (fine wiring). There are also some exceptions to this rule: some small neurons not only contribute to the local circuits, but they also send their fibers to comparatively distant brain regions. The glial differentiation brings about the stability of the microenvironment of neural tissue, communication with capillaries and the myelin formation (fixation).

Development and differentiation advance in successive steps. The pattern of development of the CA1 hippocampal region (Pokorný and Yamamoto 1981), the 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 unilateral stitching of the eye-lids in newborn kittens (Hubel and Wiesel 1970) decreases the effectivity of signal transmission on the side of deprivation. The activation effect of signals from the deprived eye on the neurons of the visual cortex became much smaller than that from the stimulated eye (Hubel and Wiesel 1976). The majority of the visual cortex neurons favored signals from the unrestricted eye (dominant position of the eye). The mechanism of eye dominance development depends on the changes of Ca^{2+} intracellular concentration (an increase in the stimulated neurons), which is related to the activation of NMDA receptors. Besides glutamate, other neurotransmitters (norepinephrine, acetylcholine and GABA) may also play an important role in the organization of neuronal networks (Ben Ari *et al.* 1990).

A comparatively short period of the developmental progress, traditionally called *critical developmental period*, is usually accompanied by increased sensitivity to both positive and negative stimuli. The most vulnerable is assumed to be the period of rapid growth (Dobbing 1968, Rodier 1994). Vulnerability is probably not directly related to the rate of growth. It is rather more associated with differentiation (plasticity) of the sensitive structures and processes in the growing and differentiating systems (Denenberg 1962). During the critical developmental period, the organizing process (morphogenetic function) (Stockard 1921) attains the threshold level and the specific stimuli of the external or internal environment, a well as an inadequate activity, may permanently alter the newly formed structures (Scott 1962, Křeček 1971, Nováková 1976). Recent findings have provided deeper understanding of this process and revealed its cellular basis. Adequate stimuli may trigger or block the expression of genetic programs for a given structure or function (Smart 1991, Litzinger *et al.* 1993). The outcome of such activity usually become stable and the structure loses its sensitivity to formerly effective specific stimuli (qualitative changes of the neuroplastic potential). The changes attained in the period of organization are therefore long-term or permanent. The functional modifications need not be immediate, but they can turn out later as a result of some subsequent developmental process, e.g. rats weaned prematurely (at postnatal day 15) can have increased salt intake exhibited after sexual maturation (Šterc *et al.* 1973). Interference with the organization process may lead to a wide spectrum of functional consequences, from modifications (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 the effects of negative stimuli (e.g. malnutrition can be partly compensated by suitable sensory stimulation – Fraňková 1977, or by rearing the young animals in an adequate social environment – Nováková 1966).

Reactive neuroplasticity

One of the possible tissue reactions to environmental changes is an immediate response limited to the period overlapping stimulus exposition. We have mentioned that various stimuli (a brief period of starvation and thirst, lesions of some CNS regions, nociceptive stimuli, parenteral administration of water) increase the resistance of the rat brain to lack of oxygen, especially in immature animals. The immature nervous tissue has the capability of responding to changes in the internal environment by adjusting its metabolism at the cellular level. This process has been called *an adaptive metabolic reaction,* because it has some aspects of both a reaction and an adaptation (Table 3). This phenomenon is accompanied by higher oxygen consumption in the altered immature nervous tissue (Trojan 1978, Pokorný and Sivenius 1995). Such higher efficacy of oxidative processes is probably based on increased potency of oxidative enzymes. The crucial element of reorganization concerns the preferential effort to

maintain proteosynthesis, which provides cells with enzymes and which is distinctly compensatory in character.

The possibility of activating the neuroplastic mechanisms by affecting the organization of the nerve system depends on the type of stimulus and on the ability of the organism to respond. A single factor may therefore have different effects during intrauterine life, after birth, during the weaning period and in adulthood. At the same time, the sensitivity of individual systems also plays an important role (Dobbing 1968, Rodier 1994). A brief period of proteosynthesis arrest (e.g. by administration of cycloheximide – Pavlík and Jelínek 1979) has a powerful effect. On the contrary, increased stimulation during early developmental stages often has opposite effects to those resulting from other forms of deprivation (e.g. in the development of the dendritic branching pattern – Greenough and Volkmar 1978). Modifications of the social milieu also have similar effect (Connor *et al.* 1981).

Table 3. Manifestations of plasticity during the development of brain

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 mainly functional	local immediate mainly metabolic	systemic with latency, long-term, both functional and structural

Table 4. Manifestations of adaptability of the nervous tissue

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

Adaptation neuroplasticity

This can be elicited by long-term or repeating stimulation. For example, long-lasting potentiation of synaptic transmission in the hippocampus (long-term potentiation – LTP) has several functional manifestations implicating changes of the parameters of transmission (Tables 3 and 4). They may bring about an increase of transmitter release or an increase in the density of postsynaptic receptors for transmitters. At the same time, long-term potentiation has also its distinct structural component (Harris *et al.* 1992, Lisman and Harris 1993). Although 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 the turnover of synaptic vesicles (Schuster *et al.* 1986). These findings support the view that the transmission changes are related to the activation of protein synthesis in the neurons involved. Proteosynthesis brings about the stabilization of structural and biochemical transformations induced by synaptic potentiation.

Long-term and complex stimuli activate neuroplastic mechanisms not only at the synaptic level, but also at the multimodular level. The altered shape and length of dendritic branches may result in the reorganization of the whole dendritic tree and consequently lead to the reorganization of afferent inputs.

The process of adaptation increases the requirements of the organism has, may it be a substance, energy or information. That is why an organism, when exposed to repeated stimuli tends to minimize losses due to such demands. This phenomenon depends on the developmental stage and on the stimulus (Table 3). The adaptive reaction occurs at the molecular level (Palkovits 1998) as well as at the level of higher brain systems (Sadato *et al.* 1996). Adaptation includes both temporary functional compensatory transformation and permanent reorganization.

Reparative neuroplasticity

The ability of the nervous tissue to recover its function damaged by intervention into the organization of the nerve tissue is considered to be one of the manifestations of neuroplasticity. As other forms of plasticity, the mechanisms of restitution are controlled by genetic programs which determine the 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 efficacy or in the number of synapses, from the rearrangement or from sprouting of dendritic and axonal branches (Björklund and Stenevi 1981). Reparation is accompanied by reorganization of local neuronal circuits, or by changes in the relation between functional brain units (Boublíková *et al.* 1991, Pokorný 1996) (Table 5). Research is therefore currently looking for a method how to reinforce the regenerative capacity of the nervous system. The intrinsic neuroplastic mechanisms may be activated by natural mechanisms or by proper medication. The „dormant" process of regeneration may become activated and bring about the recovery of injured neuronal circuits. Among the promising approaches which have been investigated, is to use the neuroplastic potential of immature neurons by their implantation into the damaged site. These neurons may help to re-establish structural and functional relations of the impaired neuronal circuits (Pokorný *et al.* 1990, 1992, Pokorný 1994, Langmeier *et al.* 1992, Trojan *et al.* 1995).

Table 5. Levels of manifestation of neuroplastic processes during reparation

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

Plastic changes may occur at three levels: synaptic level, local neuronal circuits and multimodular level (for overview see Table 6).

The synaptic level of neuroplastic changes is typical for the mechanisms of learning and memory. During learning, synaptic transmission in particular neuronal circuits is altered for a long time or permanently as a result of processing of information from the internal or external environment. As an example of this may serve the elaboration of a positive or negative phototaxic response, which brings about changes of light-induced K^+ flow and subsequently of the Ca^{2+}-dependent K^+ flow through the membrane of photoreceptors (Alcon 1984).

Table 6. Potentiality of neuroplastic processes

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"

Another example of the modulation of synaptic transmission related to learning are the changes accompanying long-term postsynaptic potentiation. In the hippocampus and in the cerebral cortex, a period of intensive electrical stimulation (tetanic stimulation) may lead to prolonged enhancement of synaptic transmission (long-term potentiation – LTP). LTP has been observed in the CA1 hippocampal pyramidal cells after tetanic stimulation of Schaffer's collaterals (Bliss and Collingridge 1993). Similar events have also been described after electrical stimulation of afferent fibers to the neurons in the visual cortex and in other regions of the brain (Grover and Teyler 1990).

Excitability changes which follow repeated stimulation (the kindling phenomenon) are associated with a sensitivity shift based either on changes in the dynamics of neurotransmitter release, on the sensitivity of receptors, or on the level of activation in the postsynaptic element. At the same time, sensitivity changes may be related to certain structural alterations (Mareš *et al.* 1981, Langmeier *et al.* 1983, Cavazos *et al.* 1994, Represa *et al.* 1993). Repeated stimulation of the sensorimotor cortex brings about an increase of seizure duration and, at the same time, it results in numerous changes in the ultrastructure of cortical synapses. Presynaptic elements were larger in volume and active zone was longer. The density of synaptic vesicles was also greater and the distribution of vesicles within the presynaptic bags was altered. Kindling phenomena were reported to be accompanied by a number of other modifications in the structure of synapses, e.g. by a decreased density of synapses with a non-perforated synaptic contact zone and an increased density of the perforated ones (Geinisman *et al.* 1988). Such findings confirm the hypothetical mechanisms of the greater efficacy of the synaptic transmission, based on changes in both the dynamics of neurotransmitter release and the level of activation of the postsynaptic elements.

The spectrum of results and theories concerning memory and synaptic plasticity is very extensive. However, it is possible to assume that short-term memory traces are induced by a sustained and specific functional activation of some neuronal circuits in the brain. These modifications are constituted primarily by ionic mechanisms and second messenger cascades induced by the activation of glutamatergic receptors

(namely NMDA). These phenomena are based upon specific gene activation and RNA formation. Specific mRNA then migrate to the potentiated synapses or dendritic spines where activated polyribosomes synthesize trophic factors, adhesion molecules and various synaptic constituents. The formation of new synaptic contacts and/or the plastic changes of existing synapses could explain long-term functional changes in synaptic activity as well as long-term memory traces (Maitre 1996)

Neuroplastic processes at the level of local neuronal circuits may follow changes in the intensity of the afferent input. For example, after partial denervation, synapses which had lost their connections degenerate, while the remaining ones with intact inputs proliferate and form new functionally active contacts in locations of those lost (Parnavelas *et al.* 1974). Reactive synaptogenesis, as well as other consequences of denervation, appears to be not only a manifestation of the ability to recover, but it also represents a general property of the nervous tissue – the ability to adjust the function to changes in the environment. That is why the increase in signal flow in particular neuronal circuits brings about corresponding memory traces (e.g. during the process of learning, during specific training, or in animals reared in a complex environment). In some cases, elevation of functional activity is followed by an associated rise of dendritic spine density and by changes in their structure (Greenough and Volkmar 1978, Mainen and Sejnowski 1996, Yuste and Tank 1996). The reorganization of neuronal circuits accompanying afferent input changes does not concern only synapses. Neuroplastic changes can be detected within the whole neuronal receptive segment, i.e. also in dendrites. The dendritic tree pattern is usually assumed to be a very stable structure. Nevertheless, even when development has terminated, some forms of increased stimulation may activate the growth and branching of the terminal dendrites (Parnavelas and Uylings 1980). Such changes in receptive segment organization may have serious after-effects for integrative properties of neurons and thus for the function of corresponding neuronal circuits (Barimega 1995, Koch 1997).

The activation of neuroplastic mechanisms at the level of neuronal circuits may become a part of neuropathological mechanisms during various diseases. Sprouting of granule cell axons which form collaterals growing back to the dentate molecular layer may serve as an example of such „aberrant plasticity" (Franck *et al.* 1995). Moreover, similar mechanisms may be responsible for other changes of the inhibition pattern. Because the newly formed collaterals of mossy fibers also form synapses with dendrites of inhibitory GABAergic basket cells, the inhibitory effect of these neurons may become more potent.

Neuroplastic processes at the multimodular level support new relations among the individual functional regions of the brain. Similarly to other forms of neuroplasticity, signal transmission and processing play major morphogenetic role. The studies of structural and functional alterations following the deprivation during development may demonstrate this hypothesis (Greenough *et al.* 1976, Greenough and Volkmar 1978, Hawrylak and Greenough 1995, Jacquin *et al.* 1995). The effects are not specific and even very different stimuli may result in similar changes. Among the deprivation stimuli, malnutrition has been most intensively studied. It represents a very complex stimulus which also includes factors other than the lack of structural, energetic or signaling material. As far as the structure of the nervous tissue is concerned, malnutrition results in a decrease of the number and length of dendritic branches, thickness of dendrites, density of dendritic spines, the length and number of axon collaterals and of synaptic density (Bedi et al. 1980). Elementary functions of nerve cells (e.g. the threshold of generalized electrical epileptic seizures, or power spectrum densities of individual EEG rhythms) as well as complex integrative functions (some parameters of memory and learning) were altered in animals exposed to malnutrition during their development (Nováková 1966, Pokorný 1977). This demonstrates that changes occur both at the local and multimodular levels.

Neuronal circuits can be modified more easily during development, usually as a response to changes in modalities of the sensory inputs. Some of the cortical regions may become more or less permanently „tuned" to the processing and analysis of a particular type of sensory signal. Such a situation becomes prominent during the development of the visual cortex. Experimental analysis of the constitution of visual performance only confirmed the clinical observations. Experiments with visual (Hubel and Wiesel 1970) and acoustic deprivation (Shirane and Harrison 1991) are accepted as classical.

A specific example of neuroplasticity at the multimodular level is the plasticity of language-sensitive centers in the human cortex. Language cortical centers can not only be modified during development, but they retain also a certain degree of plasticity in adulthood. This has been demonstrated on the variable relations of

temporal-lobe language-sensitive regions in „late" bilingual and multilingual subjects (Kim *et al.* 1997).

Mechanisms of activation and modification of neuroplasticity

A distinctive regeneration potential of CNS neurons – particularly that of the nerve stem cells – can be modified by conditions in the internal environment of the nervous tissue. Neuronal plasticity is influenced by two mechanisms (Table 7): active nerve cells produce signals which maintain the functional relations within the neuronal tissue and probably aid in its differentiation. At the same time, other signals with inhibitory effects may block these neuroplastic processes. These signals probably have both the character of bioelectrical and humoral communication. Humoral factors can bind to the extracellular matrix and become components of the neuronal microenvironment.

Table 7. Possibilities to modulate the process of neuroplasticity

REGULATION OF PLASTICITY		
active cells (neurons + glia)	*signals*	preservation of functional relations
during development		
after severance of processes	*factors*	stimulation (inhibition) of the nerve tissue growth
in pathological cases		

During development, after some of the connections had been severed, or during other pathological situations, various tissue factors may play a positive role. A substance which has both trophic effects on nerve connections, stimulates the growth of axons, and aids the growth and differentiation of the nerve tissue during development and recovery is the nerve growth factor (NGF) (Levi-Montalcini and Hamburger 1951) and other analogous agents. Such substances have both a trophic effect (they assist in the „maintenance" of nerve connections) and a growth effect (they stimulate the growth of axons). They play an important role during the proliferation and differentiation of the nerve tissue, and in processes of regeneration and recovery. They control the activity of the Na^+/K^+ ATPase membrane pump and consequent all cellular activities depending on the intracellular levels of Na^+ and K^+ or on their transmembrane gradient. This category includes the ciliary neurotrophic factor (CNTF), affecting mainly cholinergic neurons of the ciliary ganglion, the ganglionic neurotrophic factor (GNTF) stimulating neurons of sympathetic ganglia, the polyornithine-binding neurite promoting factor (PNPF) affecting spinal neurons and the spinal neurotrophic factor (SNTF) the target of which are skeletal muscle cells and glial cells of the peripheral and central nervous system (Varon and Adler 1981).

Neuroplastic processes, which are based on the formation and restoration of the fine structure of the nervous tissue, depend on the adequate supply of essential substances formed in the soma of nerve cells, which are transported by means of axonal flow to the site of proliferation – to the growth cones. Every substance which activates the anabolic functions of the soma or which maintains or accelerates axonal transport can be considered as a neurite-promoting factor (NPF – Varon and Adler 1980, 1981).

One of the principal factors which determines the effect of neuroplastic mechanisms for the maintenance or recovery of the functional and structural integrity of the nervous system is probably the actual state of the internal environment of the CNS. We can hypothesize that growth, responsiveness, adaptation and reparation are components of a single general mechanism which is based on common principles and may share various mediators and control factors.

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