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NEUROPLASTICITY: A PRINCIPLE MODEL IN VARIOUS CNS DISEASES

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ABSTRACT

Plasticity in the brain is important for learning and memory, and allows us to respond to changes in the environment. Furthermore, long periods of stress can lead to structural and excitatory changes associated with anxiety and depression that can be reversed by pharmacological treatment. Drugs of abuse can also cause long-lasting changes in reward-related circuits, resulting in addiction. Each of these forms of long-term plasticity in the brain requires changes in gene expression. Upon stimulation, second messenger pathways are activated that lead to an enhancement in transcription factor activity at gene promoters. This stimulation results in the expression of new growth factors, ion channels, structural molecules, and other proteins necessary to alter the neuronal circuit. With repeated stimulation, more permanent modifications to transcription factors are made that result in either sensitization or desensitization of a circuit. Studies are beginning to uncover the molecular mechanisms that lead to these types of long-term changes in the brain.

KEYWORDS: factors affecting; mechanisms; neuroprotection; plasticity; types.

INTRODUCTION

Neuroplasticity, also known as brain plasticity, is an umbrella term that encompasses both synaptic plasticity and non-synaptic plasticity, it refers to changes in neural pathways and synapses which are due to changes in behaviour, environment and neural processes, as well as changes resulting from bodily injury.

It is critical for learning and memory, but is also important for recovery from brain injury. It was initially believed that plasticity only occurred in developing nervous system, but is crucial to the normal function of the adult nervous system. Understanding the neural substrates and mechanisms involved in neuroplasticity improves our understanding of the fundamental and physiological basis of learning and memory. By artificially or experimentally inducing neuroplastic change, it may also be possible to develop more effective treatment regimes for various neurological disorders.

Plasticity has been demonstrated throughout the brain in various animal models. These include slice preparations of the rodent hippocampus, visual cortex and sensory cortex. Plasticity has also been demonstrated invivo, including the primate and human auditory cortex and human motor cortex. The primary motor cortex is known to be involved in higher level function rather than simply executing the movement, is a crucial site for motor learning, and is the region studied in experiments.

The boundaries of scientific topic of neuroplasticity are broadened by the fact that the term can be used operationally to cover any of the adaptive mechanisms by which the nervous system restores itself towards normal levels of functioning after injury. Neuroplasticity does not concern only the recovery of function if this latter is defined as "a return to normal or near-normal levels of performance, following the initially disruptive effects of injury to the nervous system". Neuroplasticity does not refer only to the structural and functional changes of the neuronal organization which follow an injury, but also includes the capacity of the central nervous system to adapt to new physiological conditions emerging either during its interaction with the environment. For restitution of function after nerve tissue lesions, neuroplasticity may operate by means of synaptic reorganization, through either regenerative and collateral sprouting of axons or actual recruitment of potential pre-existing connections. The latter may involve spared structures located in the affected area, i.e., intact structures temporarily excluded from their functional role which capable of reassuming their functions. Alternatively, compensation phenomena may involve structures located in undamaged areas.

TYPES OF NEUROPLASTICITY

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

Evolutionaryneuroplasticity

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. The organization of neuronal circuits has three phases. During the first phase, future neurons proliferate, in the second they migrate to the place of their destination – they assume their final size, length of processes and organization of their input and output circuits. These three development phases may overlap. The period of proliferation may differ for different cell types i.e. Periods of macroneuronal proliferation, microneuronal proliferation. 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 sysem – the long connections are formed.

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 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. This phenomenon is accompanied by higher oxygen consumption in the altered immature nervous tissue. 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 organisms 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. A brief period of proteosynthesis arrest has a powerful effect. On the contrary, increased stimulation during early development stages often forms of deprivation. Modifications of the social milieu also have similar effect.

Adaptation neuroplasticity

This can be solicited by long-term or repeating stimulation. For example, long-lasting potentiation of synaptic transmission in the hippocampus has several functional manifestations implicating changes of the parameters of transmission. 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. Although LTP does not bring about changes in the density of synaptic vesicles, the number of presynaptic investigations increases, which indicates a long-lasting increase of the turnover of synaptic vesicles. 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 organisms 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. The phenomenon depends on the developmental stage and on the stimulus. The adaptive reaction occurs at the molecular level as well as the level of higher brain systems. Adaptation includes both temporary functional compensatory transformation and permanent reorganization.

Reparative neuroplasticity

The ability of 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. Reparation is accompanied by reorganization of local neuronal circuits, or by changes in the relation between functional brain units. 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 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. 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. Plastic changes may occur at three levels: Synaptic level, Local neuronal circuits and Multimodular level.

Factors inhibiting neuroplasticity

Despite the wide variety of experimental paradigms available to induce neuroplastic change in human motor cortex, a significant impediment to their incorporation into the clinical sphere has been the large variability in effectiveness of these techniques for inducing neuroplastic change. There is little available research on the factors influencing the ability to induce neuroplastic change in human cortex. Several factors have been shown to influence a subject's response to TMS, and these can be broadly divided into extrinsic and intrinsic factors.

Extrinsic factors: These are generally associated with the subtle differences in experimental set-up. These includes: Differences in coil position, Electrode placement and Environmental stimuli. Therefore, in order to minimise the effects of extrinsic factors, the coil position needs to be continually monitored throughout experiments, and the electrodes should be positioned using a standardised set-up.

Intrinsic factors: Even if the influence of extrinsic factors is minimised, the influence of intrinsic factors cannot be as easily controlled. There are several internal factors which can potentially contribute to the variability of neuroplasticity induction between individuals, or in the same individual tested on different occasions, and these includes:Fluctuations in anatomicalvariables Fluctuations in physiological variables and Hormone fluctuations.

Fratello and colleagues were the first to investigate intra- and inter-subject variability of PAS-induced neuroplasticity. Subjects were tested on two separate occasions, and the authors reported that the overall magnitude of the induced PAS effect was reproducible across sessions, however there was very high intra-individual variability. The high variability of the induced effects was not a result of session-to-session changes in resting motor threshold, as there was high reliability in resting motor values across session.

Subject's height: Since the timing of the paired stimuli in PAS is critical to determine the direction and magnitude of the induced change, one factor that could conceivably contribute to inter-subject variability to PAS is a subject's height, more specifically the condition time to the motor cortex.

Electroencephalography (EEG) recordings were used to determine the latency of each individual's median nerve somatosensory-evoked cortical potential. This latency was used to determine the ISI in PAS protocol. However, even when individual differences in latency of the afferent volley were taken into account, this PAS protocol is still associated with significant inter-individual variability.

Neuromodulator fluctuations: Physical activity can increase levels of brain derived neurotrophic factor (BDNF), which has an important influence on neuronal plasticity. For example, BDNF knockout mice show impaired LTP induction in the CA1 region of hippocampus. In addition, short period of exercise enhances cognitive function in rats, and in associated with elevated levels of BDNF.

Fluctuations in physiological variable: Another factor that has not been investigated to date, but is likely to contribute significantly to the variability associated with neuroplasticity induction is circadian variation in various hormone levels.

Factors enhancing neuroplasticity

Sensorimotor pathways and recovery: The principle motor cortex has separate clusters of output neurons that can facilitate the same spinal motor neuron. Also, a single cortical motor cell can project to the spinal motor neurons for several muscles, even those that might act across a joint. This overlapping organization contributes to the control of the complex muscle synergizes for the voluntary movement. In humans, cortical sensory organization has occurred within four weeks after amputation of an arm. When the patients face was touched,

the patient experienced the sensation in the missing hand, suggesting that the sensory input from the face had invaded the cortical hand area. This plasticity probably arises by the unmasking of previously silent synapses from thalamocortical and intracortical circuits that are mediated by acetylcholine and norepinephrine, but in some instances might arise from the sprouting of dendrites over short distances.

Descending pathways: In primates, cortical, thalamic, limbic, and brainstem signals feed into the basal ganglia and contribute to a motor behaviour by direct projections to the midbrain motor region and by indirect projections to the thalamus. The basal ganglia influence motor circuits through their myriad miniloops to help specify the combination, sequence, and direction of movements. These parallel arrangements occur in cerebellar and most other sensory and motor projections.

Neurotransmitter effects on recovery: After being given dextroamphetamine, rats and cats that underwent a unilateral or bilateral ablation of the sensorimotor or frontal cortex had more rapid recovery of the ability to walk across a beam than did controls. Neurotransmitters, including acetylcholine, norepinephrine, dopamine, and serotonin, have enhanced motor recovery.

Biologic mechanisms of restoration: Motor learning can produce the arborisation of dendrites and the growth of synapses in the cerebral and cerebellar cortex in animals. After a unilateral injury to the sensorimotor cortex serving the forelimb of adult rats, one study showed the growth of neuronal dendrites in the sensorimotor cortex of the normal opposite side.

Possible therapies for molecular biology and biotechnology: Tissue culture and vertebrate model have shown that substances in the extracellular matrix tend to inhibit axonal elongation at the site of injury. Direct transplantation of motor neurons and cells that produce a specific neurotransmitter to replace lost adrenergic projections has met with some success. The techniques to manipulate the promoters and inhibitors of neuroplasticity are still in early development.

MOLECULAR AND CELLULAR MECHANISM OF NEUROPLASTICITY

The mechanisms of synaptic and morphological plasticity have been extensively studied in the context of their contribution to learning and memory. We emphasize some of the common

themes in studies of synaptic and structural plasticity, and some of the specific molecular players most cogent to a subsequent discussion of the mechanisms of antidepressant response.

A common theme is that many forms of synaptic potentiation are triggered (fig. 1) by increases in synaptic calcium influx and in the local concentration of the second messenger molecule cyclic AMP (cAMP). Local calcium influx, for example, commonly derives from the NMDA receptor, which is a highly evolved coincidence detector—it is activated only when presynaptic and postsynaptic cells are depolarized simultaneously. cAMP is regulated by many modulatory neurotransmitters, including serotonin, dopamine, and norepinephrine, as well as by calcium; it is therefore optimally suited for the integration of synaptic events with the modulatory influences of global variables such as arousal and attention. Upon induction by a sufficient rise in the local concentration of calcium, it can phosphorylate itself. Autophosphorylated CaMKII is persistently active, even after calcium levels fall. Several other calcium-calmodulin kinases exists in neurons. CaMKIV, in particular, is prominent in the neuronal nucleus, where it is an important activator of regulated transcription factor such as CREB.

Both CaMKII and other kinases can phosphorylate the GluR1 subunit of the AMPA glutamate receptor and associated proteins. This phosphorylation both increases the number of AMPA receptors in the postsynaptic membrane (by triggering insertion of new AMPA receptors) and enhances the function of those receptors already inserted. Both mechanisms contribute to an enhancement of synaptic strength. At the structural level, insertion of AMPA receptors can result in the activation of ‘silent synapses’. . Upon the induction of LTP, AMPA receptors are inserted into the postsynaptic membrane at such a synapse, rendering it active upon subsequent single presynaptic impulses (hence no longer ‘silent’). This unsilencing of silent synapses contributes to synaptic strengthening and appears to be a major mechanism of LTP.

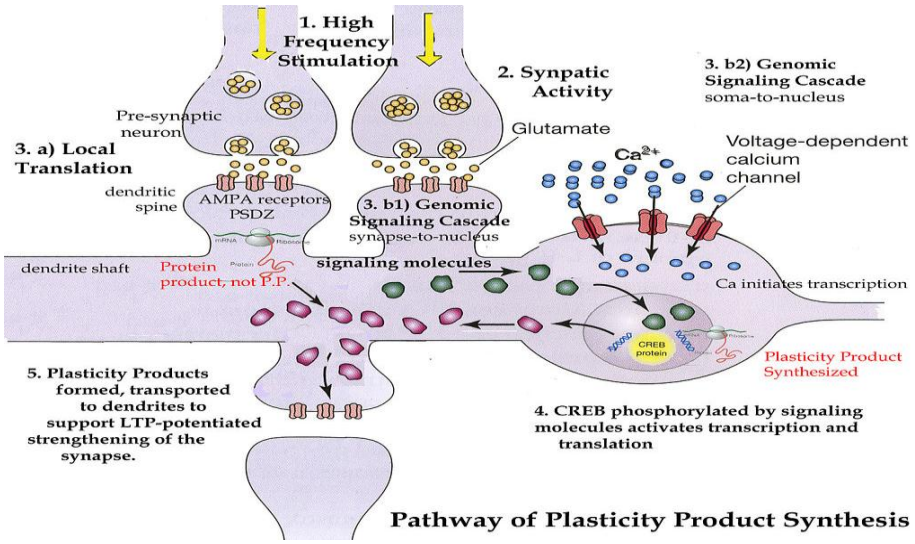

Fig. 1: mechanism of activation and modification of neuroplasticity

During development, after some of the connections had been served, 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 and other analogous agents. Such substances have both a both trophic effect and a growth effect. 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 neurotophic 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.

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 the cell, 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.

One of the principle 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 mechanisms which is based on common principles and may share various mediators and common factors.

ROLE OF NEUROPLASTICITY IN PHYSIOLOGICAL AND PATHOLOGICAL CONDITION

Neuroplasiticity In Physiological Conditions

Neuroplasticity is brought about by several mechanisms. These changes can be caused by several events including an increase in excitatory neurotransmitter release or a reduction of tonic inhibition. Studies on rodents have found that the administration of the GABA antagonist bicuculline results in both rapid changes in the cortical representation of M1, and an increase in the strength of synaptic connections in M1, indicating that GABAergic neurons play a critical role in modulating plasticity. Human studies support the animal experiments and have clearly demonstrated that a reduction of GABA –mediated inhibition facilitates neuroplastic change in primary motor cortex. A increase in synaptic efficacy is referred to as long-term potentiation(LTP), and requires high-frequency stimulation of excitatory afferents. A decrease in synaptic efficacy can also be induced with lower frequencies, and is referred to as long-tern depression(LTD).

The form of potentiation can be broadly divided into potentiation that is either N-methyl-D-aspartate (NMDA) receptor-dependent or –independent. The NMDA receptor plays an important role in the induction of NMDA receptor dependent potentiation due to its unique structural and functional characteristics (fig.2). Specifically, the NMDA receptor is a ligand-gated (glutamate) ion channel that is blocked by Mg2+ in a voltage-dependent manner. This characteristic of the NMDA receptor helps explain the properties of activity-dependent LTP.

NMDA receptor consists of mainly five binding sites as, modulatory site, zinc modulatory site, glycine binding site, glutamate binding site and magnesium binding site. When, glycine and glutamate binds the receptor, it leads to calcium and sodium ions influx and potassium eflux. the level of depolarization of the NMDA receptor needs to reach a critical threshold level to expel the Mg2+, for induction of LTP, which is a function of not only the stimulus intensity, but also the pattern of stimulation.

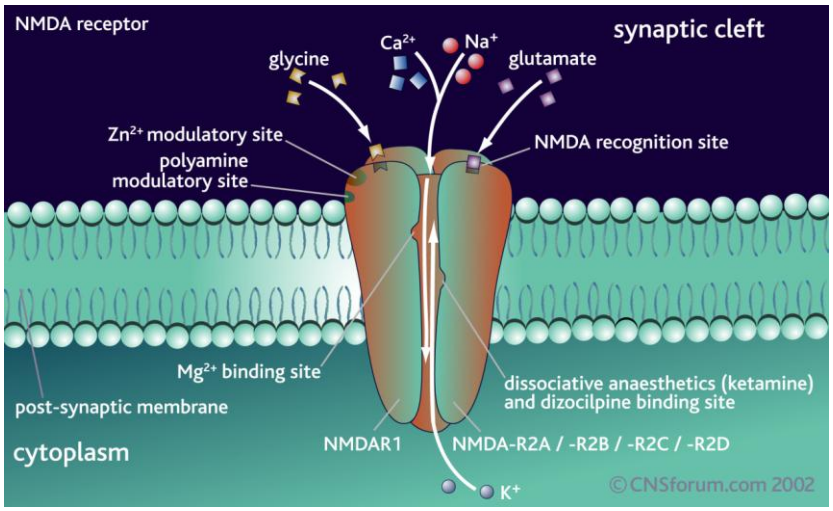

Fig. 2: neuroplasticity in pathological conditions

Parkinson's disease

Parkinson's disease results from greatly reduced activity of dopamine secreting cells caused by the **cell death** in the pars compacta region of the substansia nigra, death in the substansia nigra and ventral (front) part of the pars compacta. Their is neuronal loss and lewy bodies deposition seen in parkinson's disease. Neuronal loss is accompanied by death of astrocytes (star-shaped glial cells) and activation of the microglia (another type of glial cell).

Mechanisms of brain cell death: (fig. 3)

Accumulation of protein: Accumulation of alpha-synuclein protein bound to ubiquitin in the damaged cells. This insoluble proteins accumulates inside neurons forming inclusions called lewy bodies. This lewy bodies first appears in the olfactory bulb, medulla oblongata and potine tegmentum.

Proteosomal and lysosomal system dysfunction and reduced mitochondrial activity: In this, their is an iron accumulation in substansia nigra in conjunction with protein inclusions like lewy bodies. It may be related to oxidative stress, protein aggregation and neuronal death.

Glutamate binds to NMDA receptor, leads to calcium influx. This calcium ions releases nitric oxide synthase enzyme, and forms nitric oxide. These leds to formation of reactive oxidative species like PINK 1 and DJ1, which leads to Cytochrome C to caspase activation further leading to apoptosis.

Neuroplasticity is the changes in the brain connections that restores or compensates for lost function. For these, daily exercise is the best option for treating parkinson's disease. Goals of **Physical therapy are:** Slow sensorimotor deterioration, Prevent falls, Establish home exercise program that challenges the person with PD, Follow up every 3-6 months.

Exercise leads to many advantages like: Protection of viable dopamine neurons (neuroprotection), Restoring compromised neural pathways. (neuroplasticity), Increasing reliance on undamaged systems. (neuroplasticity)

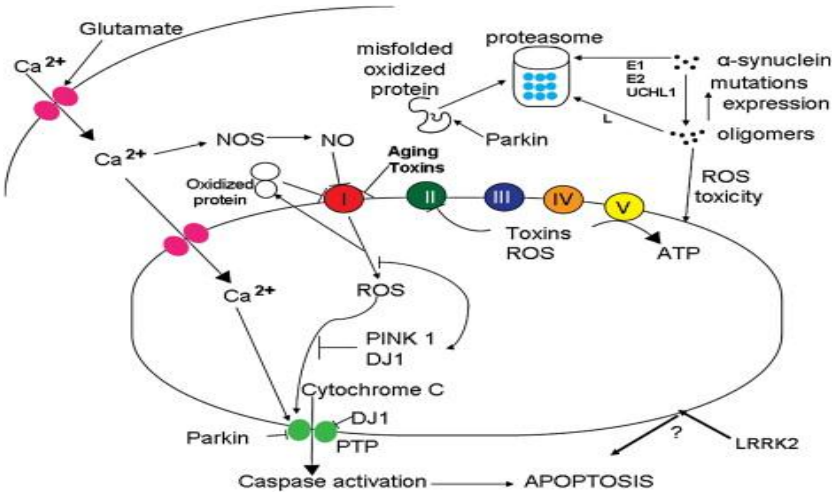

Fig. 3: techniques of induction of neuroplasticity

Repetitive peripheral stimulation: The main technique for inducing neuroplastic change in M1 is by pairing a peripheral electrical stimulus with TMS to the contalateral motor cortex. The peripheral electrical stimulus was delivered to the median nerve at the wrist, which is a mixed nerve, and provides motor innervation of the abductor pollicis brevis muscle. A single-pulse suprathreshold TMS was delivered to the contralateral M1 at varying ISIs following the peripheral stimulus. The study confirmed that the maximum increase in cortical excitability following PAS occurred with an ISI of 25 ms. Importantly, the study also demonstrated that a shorter ISI of 10 ms produced significant inhibition of MEP amplitude.

Repetitive cortical stimulation: Another experimental paradigm for inducing persistent changes in cortical excitability is transcranial direct current stimulation. A pair of saline-soaked surface electrodes are placed on the scalp, with the stimulation electrode placed over the motor cortical representational field of the target muscle, and the other electrode placed over the contralateral orbit. This form of stimulation can produce both decreases and increases in cortical excitability, with the direction of change in cortical excitability

dependent on whether the stimulation is cathodal or anodal. Cathodal stimulation result in a decrease in cortical excitability, while anodal stimulation has the opposite effect. The exact mechanism for these induced changes is still not clear, however it seems likely that the direct-current induces changes in resting membrane potential that results in a change in NMDA-receptor activation.

Repetitive combined peripheral and cortical stimulation: This can involve repeated electrical stimulation of the afferent nerve or motor point, or vibration of the muscle. These techniques involve TMS (rTMS), however the techniques differ in terms of the frequency, duration and intensity of stimulation. Depending on the frequency of stimulation, rTMS can either enhance or depress cortical excitability. The increase in cortical excitability outlasts the period of stimulation. In general, low frequency stimulation depresses cortical excitability, whereas high frequency stimulation enhances cortical excitability. The mechanisms responsible for the induced changes in the cortex are not entirely clear. Modification of synaptic efficacy appears a likely candidate mechanism. This is because the induced effects outlast the period of stimulation, the effects induced obey the "homeostatic plasticity" principle and finally, the increase in cortical excitability is associated with a reduction in GABAa-mediated inhibition.

INHIBITION OF NEUROPLASTICITY: SCHIZOPHRENIA

The disease process of schizophrenia appears to involve deficient glutamate-mediated excitatory neurotransmission through the NMDA receptors. Hypoactivation of only NMDA receptors in schizophrenia is unlikely to result from deficits in glutamate release because, in the adult monkey DLPFC, both AMPA and NMDA receptors mediate fast synaptic transmissions at glutamate synapses; thus, decreased glutamate release would also result in deficits in AMPA receptor-mediated transmission. It is possible, however, the NMDA hypoactivity in schizophrenia is associated with decreased levels of synaptic NMDA receptor proteins in particular classes of inputs that are difficult to detect. In the DLPFC, pyramidal neurons are the principle source of the glutamate transmissions, as well as the targets of the majority of glutamate containing axon terminals. Although the number of these neurons does not appear to be altered in schizophrenia, neuronal density in the DLPFC and certain other cortical regions, such as the primary visual cortex, has been reported to be increased in schizophrenia. So there is need for decreased neuroplasticity in schizophrenia. This findings

have raised series of questions regarding the neuroplastic nature of the apparent changes in spine density in schizophrenia.

CLINICAL CORRELATES OF NEUROPLASTICITY

Clinical correlation means that something notable was found on diagnostic imaging but it may not be meaningful for patient. It is checking the history and physical to see if the notable finding has any meaning in the patients life.

Hydrocephalus: Clinical, electrophysiological and metabolic studies are required with specific focus on the reasons for the improved noted after surgical treatment of hydrocephalus. Non-invasive methods (such as isotopic imaging) are recommended for such investigations. To compliment this clinical syudies, animal models of hydrocephalus should be employed to study the effects of the enlarged ventricles on the brain by histological, metabolic and functional criteria. New pharmacological approaches should be sought in order to alleviate this condition.

Chronic spinal cord and brain compression: These clinical states also provides good clinical models for experimental studies for neuroplasticity. The experimental methods to be considered for these studies should include: quantative immunohistochemical techniques, metabolic studies, computed topography, radiotracer techniques, nuclear magnetic resonance, and blood flow measurements. These studies are needed in order to select simpler techniques for treatment and to identify prognostic indicators for the total management of these disorders.

Rehabilitation: One of the prerequisites for the successful rehabilitation of patients with moderately severe brain injury is adequate management of diseases during its primary and secondary stages. Methods should be sought for the adequate diagnosis and treatment of head injuries in various parts of the world.

FUTURE PROSPECTIVES

It is evident that recent scientific developments in the understanding of neuroplasticity have important implications for the diagnosis and treatment of disorders of the central nervous system in man. It is obvious that the neurons of the mammalian central nervous system have a marked capacity for regeneration. The main practical goal must now be to harness this capacity for the purpose of functional recovery.

The rapid development of neuroscientific studies in the field of neuroplasticity is likely to lead to the better management of brain and spinal cord lesions in man. The development of relevant experimental strategies will be highly dependent on the contribution of clinical studies in man.

Two important aspects that need to be explored are: The diagnosis and management of craino-spinal trauma and its various facets of specific relevance to particular geographical areas of the world; and The role of environmental factors (e.g. nutrition, toxins, and infection disorders) in limiting the capacity for repair of the human nervous system.

In recent years, important research has been carried out on the following topics: Synaptic connections and transmitter systems, The regenerative capacity of central neurons after experimental injury, The immunocytochemistry of central neurons, The regenerative capacity of central neurons as revealed by grafting experiments, Monoamine grafts in the striatum, The effect of ganglioside treatment on the plastic responses of central neurons after deafferentation.

CONCLUSION

Neuroplastic mechanisms are important both in the genesis of disorders and disease of the nervous system and for its repair after different types of damage and trauma. Modulation of neuroplastic mechanisms by physical and chemical agents would appear to be one of the most powerful therapeutic tools of restorative neurology.

REFERENCES

1. Buijs RM, van Eden CG, Goncharuk VD, Kalsbeek A. The biological clock tunes the organs of the body: timing by hormones and the autonomic nervous system. J Endocrinol., 2003; 177: 17-26.
2. Datta AK, Harrison LM, Stephens JA. Task-dependent changes in the size of response to magnetic brain stimulation in human first dorsal interosseous muscle. J Physiol., 1989; 418: 13-23.
3. Martin v sale Bsc (hons), bappsci (physio) Factors influencing the Induction of neuroplastic Changes in human motor cortex A thesis submitted for the degree of Doctor of philosophy.
4. Goldberg JF, Harrow M.Bipolar Disorders: Clinical Course and Outcome. American Psychiatric Press: Washington, DC, 1999.

5. Goodwin FK, Jamison KR.Manic-depressive Illness. Oxford Uni-versity Press: New York, 1990.
6. HK Manji, GJ Moore, G Rajkowska and G Chen, Neuroplasticity and cellular resilience in mood disorders, molecular psychiatry., 2000; 5: 578 – 593.
7. S. Trojan, J. Pokorny, Theoretical aspects of Neuroplasticity, Physiological research, 0862 – 8408.
8. CONNOR JR, DIAMOND MC, CONNOR JA, JOHNSON RE: A Golgi study of dendritic morphology of the occipital cortex of socially reared aged rats. Exp Neurol, 1981; 73: 525 – 538.
9. DENNENBERG VH: An attempt to isolate critical periods of development in the rats. J Comp Physiol Psychol., 1962; 55: 813-815.
10. DOBBING J: Vulnerable periods in developing brain. In: Applied Neurochemistry. AN DAVISON, J DOBBING, (eds), Blackwell, Oxford, 1998; 287-316.
11. HARRIS KM, JENSEN FE, TSAO B: Three diamensional structure of dendritic spines and synapses in rat hippocampus (CAI) at postnatal day 15 and adult age: implications for the maturation of synaptic physiology and long-term potentiation. J Neurosci., 1992; 12: 2685-2705.
12. LANGMEIER M, MARES J, POKORNY J: Endocytotic activity of the presynaptic membrane and the morphometric differences of cortical synapses during the excitability changes in the initial phases of kindling. J Hirnforsch., 1992 33: 249-259.
13. LISMAN JE, HARRIS KM: Quantal analysis and synaptic anatomy – integrating two views of hippocampal plasticity. Trends Neurosci., 1993; 16: 141-147.
14. NOVAKOVA V: Time of weaning: Its effect on the Rat Brain. Academia, Prague, 1976; 7-11.
15. PALKOVITS M: Plasticity of central nervous system neurons: expression of transmitters and co-transmitters in neuronal cells. 9th Int Congr Czech Slovak Neurochem Soc, 1998; 17.
16. PAVLIK A, JELINEK R: Effects of cycloheximide administered to rats in early postnatal life: correlation of brain changes with behaviour in adulthood. Brain Res., 1979; 167: 200-205.
17. POKORNY J: Hippocampal granular layer lesion: replacement of lost neurons by the implantation of embryonal nerve tissue suspension. Physiol Res., 1994; 43: 269.
18. POKORNY J, SIVENIUS J: Sensitivity to global brain ischaemia during postnatal development of rats. Physiol Res., 1995; 44.

19. POKORNY J, LANGMEIER M, TROJAN S: Transplantation into the hippocampus: estimation of the number of surviving neurons. Physiol bohemoslov., 1990; 39: 564.
20. POKORNY J, LANGMEIER M, TROJAN S: Are embryonal neurons used for transplantation "sufficiently immature"? Physiol Res., 1992; 41: 459-462.
21. RODIER PM: Vulnerable periods and processes during central nervous system development. Environ Health Perspect., 1994; 102(2): 121-124.
22. ADATO N, PASCUAL-LEONE A, GRAHMAM J, IBANEZ V, DEIBER MP, DOLD G, HALLET M: Activation of the primary visual cortex by Braille reading in blind subjects. Nature., 1996; 380: 526-527.
23. SCOTT JP: Critical periods in behavioural development. Science., 1962; 138: 949-951.
24. SCHUSTER T, KRUG M, PLASCHKE M, SCHULZ E, WENZEL J: Ultrastructural changes in neurons and synapses of the dentate area following long-term potentiation – a morphometric study. In: Learning and memory. H MATTHIES (eds), Pergamon Press, Oxford, 1986; 115-118.
25. STOCKARD CR: Development rate and structural expression: an experimental study of twins, "double monsters" and single deformities, and the interaction among embryonic organs and development. Am J Anat., 1921; 28: 115-263.
26. TROJAN S: Adaptation of the central nervous system to oxygen deficiency during ontogenesis. Acta Univ Carol Med Monographia Vol 85, Prague, 1978.
27. TROJAN S, POKORNY J, LANGMEIER M, NARES J: The degree of maturation of embryonal neurons in the suspension used for neurotransplantation (in Czech). Sborn Lek., 1995; 96: 157-162.
28. Donoghue JP, Suner S, Sanes JN: Dynamic organization of primary motor cortex output to target muscles in adult rats – rapid reorganization following motor nerve lesions. Exp Brain Res, 1990; 79: 479-503.
29. Pons TP, Garraghty PE, Ommaya AK, Kaas JH, Taub E, Mishkin M: Massive cortical reorganization after sensory deafferentation in adult macaques. Science., 1991; 252: 1857-1860.
30. Sanes JN, Wang J, Donoghe J: Immediate and delayed changes of rat motor cortical output representations with new forelimb configurations. Cerebral cortex., 1992; 2: 141-152.
31. Ramachandran VS, Roger-Ramachandran DC, Stewart M: Perpetual correlates of massive cortical reorganization. Science., 1992; 258: 1159-1160.

32. Dykes R, Metherate R: Sensory cortical reorganization following peripheral nerve injury, In Finger S, Levers T, Almi C, Stein D (Eds): Brain injury and recovery. New York, NY, Plenum Press, 1988; 213-254.
33. Whishaw IQ, Pellis SM, Gorny BP, Pellis VC: The impairments in reaching and the movements of compensation in rats with motor cortex lesions: An endpoint, videorecording, and movement notation analysis. Behave Brain Res, 1991; 42: 77-91.
34. Strick P: Anatomical organization of multiple motor areas in the frontal lobe, In Waxman S(Ed): Functional Recovery in Neurological Disease. New York, NY, Raven Press, 1988; 293-312.
35. Chevalier G, Deniau JM: Disinhibition as a basic process in the expressions of striatal functions. Trends Neurosci., 1990; 13: 277-280.
36. Jones E: Ascending inputs to, and internal organization of, cortical motor areas, In Porter R (Ed): Motor Areas of the Motor cortex. New York, NY, Wiley, 1987; 21-29.
37. Sutton RL, Hovda DA, Feeney DM. Amphetamine accelerates recovery of locomotor function following bilateral frontal cortex ablation in cats. Behav Neurosci., 1989ug; 103(4): 837–841.
38. Crisostomo EA, Duncan PW, Propst M, Dawson DV, Davis JN. Evidence that amphetamine with physical therapy promotes recovery of motor function in stroke patients. Ann Neurol., 1988 Jan; 23(1): 94–97.
39. Connor JR, Diamond MC. A comparison of dendritic spine number and type on pyramidal neurons of the visual cortex of old adult rats from social or isolated environments. J Comp Neurol., 1982 Sep 1; 210(1): 99–106.
40. Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc Natl Acad Sci U S A., 1990 Jul; 87(14): 5568–5572.
41. Jones TA, Schallert T. Overgrowth and pruning of dendrites in adult rats recovering from neocortical damage. Brain Res., 1992 May 22; 581(1): 156–160.
42. Aguayo AJ, Rasminsky M, Bray GM, Carbonetto S, McKerracher L, Villegas-Pérez MP, Vidal-Sanz M, Carter DA. Degenerative and regenerative responses of injured neurons in the central nervous system of adult mammals. Philos Trans R Soc Lond B Biol Sci., 1991 Mar 29; 331(1261): 337–343.
43. Tessler A. Intraspinal transplants. Ann Neurol., 1991 Feb; 29(2): 115–123.

44. Schnell L, Schwab ME. Axonal regeneration in the rat spinal cord produced by an antibody against myelin-associated neurite growth inhibitors. Nature. 1990 Jan 18; 343(6255): 269–272.
45. Yakovleff A, Roby-Brami A, Guezard B, Mansour H, Bussel B, Privat A. Locomotion in rats transplanted with noradrenergic neurons. Brain Res Bull. 1989 Jan; 22(1): 115–121.
46. Clowry G, Sieradzan K, Vrbová G. Transplants of embryonic motoneurones to adult spinal cord: survival and innervation abilities. Trends Neurosci. 1991 Aug; 14(8): 355–357.
47. LEVI-MONTALCINI R, HAMBURGER V: Selective growth stimulating effects of mouse sarcoma on the sensory and sympathetic nervous system of the chick embryo. J Exp Zool, 1951; 116: 321-361.
48. VARON S, ADLER R: Nerve growth factors and control of nerve growth, Curr Top Dev Biol, 1980; 16: 207-252.
49. VARON S, ADLER R: Trophic and specify ing factors directed to neuronal cells. Adv Cell Neurobiol., 1981; 2: 115-163.
50. Jacobs KM, Donoghue JP. Reshaping the cortical motor map by unmasking latent intracortical connections. Science., 1991; 251: 944-947.
51. Malinow R, Mainen ZF, Hayashi Y. LTP mechanisms: from silence to four-lane traffic. Curr Opin Neurobiol., 2000; 10: 352-357.
52. Kaas JH. Plasticity of sensory and motor maps in adult mammals. Annu Rev Neurosci., 1991; 14: 137-167.
53. Hess G, Donoghue JP. Long-term potentiation of horizontal connections provides a mechanism to reorganize cortical motor maps. J Neurophysiol., 1994; 71: 2543-2547.
54. Ziemann U, Muellbacher W, Hallett M, Cohen LG. Modulation of practice-dependent plasticity in human motor cortex. Brain., 2001; 124: 1171-1181.
55. Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol., 1973; 232: 331-356.
56. Dudek SM, Bear MF. Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci U S A., 1992; 89: 4363-4367.
57. Davies CH, Starkey SJ, Pozza MF, Collingridge GL. GABA autoreceptors regulate the induction of LTP. Nature., 1991; 349: 609-611.

58. Aroniadou VA, Keller A. Mechanisms of LTP induction in rat motor cortex in vitro. Cerebral Cortex., 1995; 5: 353-362.
59. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature., 1993; 361: 31-39.
60. Andersen P, Sundberg SH, Sveen O, Wigstrom H. Specific long-lasting potentiation of synaptic transmission in hippocampal slices. Nature., 1977; 266: 736-737.
61. Turrigiano GG, Nelson SB. Thinking globally, acting locally: AMPA receptor turnover and synaptic strength. Neuron., 1998; 21: 933-935.
62. Cohen LG, Bandinelli S, Topka HR, Fuhr P,Roth BJ, Hallett M. Topographic maps of human motor cortex in normal and pathological conditions: mirror movements, amputations and spinal cord injuries. Electroencephalogr Clin Neurophysiol Suppl, 1991b; 43: 36-50.
63. Ziemann U, Hallett M, Cohen LG. Mechanisms of deafferentation-induced plasticity in human motor cortex. J Neurosci, 1998b; 18: 7000-7007.
64. Rosenkranz K, Rothwell JC. Differential effect of muscle vibration on intracortical inhibitory circuits in humans. J Physiol, 2003; 551: 649-660.
65. Kaelin-Lang A, Luft AR, Sawaki L, Burstein AH, Sohn YH, Cohen LG. Modulation of human corticomotor excitability by somatosensory input. J Physiol., 2002; 540: 623-633.
66. Lang N, Nitsche MA, Paulus W, Rothwell JC, Lemon RN. Effects of transcranial direct current stimulation over the human motor cortex on corticospinal and transcallosal excitability. Exp Brain Res., 2004; 156: 439-443.
67. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol., 2000; 527 Pt 3: 633-639.
68. Gonzalez-Burgos G, Kroener S, Zaitsev AV, Povysheva NV, Krimer LS, Barrionuevo Get al (2007b). Functional maturation of excitatory synapses in layer 3 pyramidal neurons during postnatal development of the primate prefrontal cortex. CerebCortex (in press; E-pub ahead of print).
69. Akbarian S, Sucher NJ, Bradley D, Tafazzoli A, Trinh D, Hetrick WP et al (1996). Selective alterations in gene expression of NMDA receptor subunits in prefrontal cortex of schizophrenics.J Neurosci16: 19–30.
70. Glantz LA, Lewis DA. Reduction of synaptophysin immunoreactivity in the prefrontal cortex of subjects with schizophrenia: regional and diagnostic specificity.Arch Gen Psychiatry, 1997; 5: 943–952.

71. Mirnics K, Middleton FA, Marquez A, Lewis DA, Levitt P (2000). Molecular characterization of schizophrenia viewed by micro-array analysis of gene expression in prefrontal cortex. Neuron, 2000; 28: 53–67.
72. Black JE, Kodish IM, Grossman AW, Klintsova AY, Orlovskaya D, Vostrikov V et al. Pathology of layer V pyramidal neurons in the prefrontal cortex of patients with schizophrenia. Am J Psychiatry, 2004; 161: 742–744.
73. Benes FM, Vincent SL, Marie A, Khan Y. Up-regulation of GABA-A receptor binding on neurons of the prefrontal cortex in schizophrenic subjects. Neuroscience, 1996; 75: 1021–1031.
74. Akbarian S, Kim JJ, Potkin SG, Hagman JO, Tafazzoli A, Bunney J WE et al. Gene expression for glutamic acid decarbox-ylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. Arch Gen Psychiatry, 1995; 52: 258–266. This study provided the seminal evidence for a deficit of GABA synthesis in schizophrenia and that this alteration might be cell type-specific.
75. Ohnuma T, Augood SJ, Arai H, McKenna PJ, Emson PC. Measurement of GABAergic parameters in the prefrontal cortex in schizophrenia: focus on GABA content, GABAA receptor a-1 subunit messenger RNA and human GABA transporter-1 (HGAT-1) messenger RNA expression. Neuroscience., 1999; 93: 441–448.
76. Simpson MDC, Slater P, Deakin JFW, Royston MC, Skan WJ. Reduced GABA uptake sites in the temporal lobe in schizophrenia. Neurosci Lett., 1989; 107: 211–215.
77. World Health Organization, Geneva 1983, Neuroplasticity and repair in the central nervous system.