

Introduction

CHAPTER I

Introduction

Stroke is a major public health problem. It is the third leading cause of death in the United States and the second leading cause of death in the developing countries. Stroke is also responsible for a large proportion of the problem of neurological disorders. It is often disabling than fatal. Stroke is the leading cause of severe neurological disability and results in enormous cost and loss of productivity. The World Health Organization has defined stroke as “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.” (Cauraugh et al., 2010).

Stroke survivors have approximately two thirds of residual neurological deficits that impair function. Dysfunction from upper extremity (UE) hemiparesis specifically, impairs performance of many daily activities and reduces functional independence. Stroke rehabilitation usually focuses traditionally on the first three to six months after stroke. Rehabilitation consists largely of passive (nonspecific) movement approaches, or compensatory training of the nonparetic arm. The functional gains and possible neural plasticity can occur, via active practice, long after spontaneous recovery would be expected to end (Whitall et al., 2000).

Neural plasticity or Neuroplasticity (also variously referred to as brain plasticity, cortical plasticity or cortical re-mapping) refers to the changes that occur in the organization of the brain and nervous system as a result of experience. The concept of neuroplasticity focuses on, the brain areas are still re-wiring in response to changes in the environment. The agreement in the past decades was that lower brain and neocortical areas were immutable after development. The hippocampus and dentate gyrus, which are areas related to memory formation, where new neurons continue to be produced into adulthood, are highly plastic. The environmental changes could alter behavior and cognition by modifying connections between existing neurons and via neurogenesis in the hippocampus and the cerebellum (Stein and Hoffman, 2003).

The substantial changes usually occur in the lowest neocortical processing areas. These changes can profoundly alter the pattern of neuronal activation in response to experience. According to the theory of neuroplasticity, thinking, learning, and acting actually change both the brain's physical structure, or anatomy, and functional organization, or physiology from top to bottom. Today neuroscientists believe that the brain is not immutable after the development but

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it continues to change and develop neuroplasticity. This means that both structural and functional aspects of the brain are flexible (**Stein and Hoffman, 2003**).

A series of bilateral training robotic studies on stroke patients during the chronic recovery phase showed more improvement of the affected upper limb in comparison to unilateral training and control groups. Moving two arms concurrently produces an interlimb coupling and the arms typically more conform to temporal and spatial symmetry constraints than unilateral training. Bilateral arm training (BAT) involves repetitive practice of symmetrical bilateral movements in different forms. Bilateral isokinematic training, which involves spatiotemporally identical movements with functional activities, and robot-assisted movement training involving assistive exercise on the arm trainer with or without auditory or visual cueing are examples of BAT. It was assumed that symmetrical bilateral movements activate similar neural networks in both hemispheres when homologous muscle groups are simultaneously activated. Bilateral symmetrical movements cause activation of the undamaged hemisphere. It promotes the neural plasticity and increase the activation of the damaged hemisphere. It facilitates also the movement control of the impaired limb (**Lin et al., 2010**).

Statement of the problems

- Which type of the upper limb training (unilateral or bilateral upper limb training) could be the best physical training on improving the motor function of the affected upper limb and also on the neural plasticity in the chronic stroke patients?
- Is there a significant effect when adding weight to the non affected arm on the motor performance of the affected upper limb and also on the brain excitability (neural plasticity) in the chronic stroke patients?
- Which type of the upper limb training (unilateral or bilateral upper limb training) has an immediate and long term(retention) effect on the motor performance of the affected upper limb and also on the neural plasticity in the chronic stroke patients?

Purposes of the study

- To compare the physical and the neurophysiological effects of using different methods of physical therapy training (unilateral training of the upper limb and bilateral upper limb training) on the brain excitability in different areas of both

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hemispheres in the chronic stroke patients and consequently on the motor performance of the affected upper limb.

- To determine the effects of adding weight during the bilateral upper limb training on the brain excitability in different areas of both hemispheres in the chronic stroke patients and consequently on the motor performance of the affected upper limb.
- To determine the immediate and long term effects of different upper limb training programs on the neural plasticity and consequently on the motor performance of the affected upper limb in the chronic stroke patients.

Significance of the study

Stroke is one of the leading causes of disability in the older population. It affects aspects of a person's physical, emotional, and social life. Stroke mortality rates decline and at the same extent, individuals are more likely to have residual impairments that could affect daily living. More than 80% of individuals with stroke experience hemiparesis, and of those people who initially have upper-extremity paresis, 70% appear to have a residual impairment. The upper limb impairments can compromise participation in many essential and meaningful tasks. Return of upper-limb function has been identified as an important rehabilitation goal (**Liepert, 2006; Mehta et al., 2007**).

Upper limb dysfunction in stroke patients is characterized by paresis, loss of manual dexterity and movement abnormalities that impact on the performance of activity of daily living (ADLS). The ultimate goal for many stroke patients is to achieve maximum level of functional independence that enables them to return home and reintegrate into community life as fully as possible. Stroke rehabilitation is often described as a process of active (motor) learning that starts, preferably, within the first few days after the stroke. Some trials found that the favourable outcome in the ADL and independence is still significant at ten years post-stroke onset not only in the first six months (**Ward et al., 2003**).

Research in neural plasticity of adult cortical representations brought the hope of significant potential for further improvement in therapy after cerebrovascular stroke. The processes involved in plasticity also give an important message for clinical rehabilitation of chronic stroke patients. Application of the results from neurophysiology and functional brain

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imaging research into the clinical practice is in the initial stages and remains a challenge for the future in the rehabilitation of chronic stroke patients (**Hlustík and Mayer, 2006**). Motor cortex disinhibition presents in the affected hemisphere before the physical therapy program. Bilateral arm training and task specific training could affect this disinhibition and may have an effect on the degree of brain plasticity especially for the chronic stroke patients (**Cauraugh and Summers, 2005 ;Liepert , 2006**).

Null hypothesis

- There is no significant effect of using different forms of upper limb training on the brain excitability in different areas of both hemispheres in the chronic stroke patients and consequently on the motor performance of the affected upper limb.
- Weight on the non affected arm during bilateral upper limb training does not have an adding significant effect on the brain excitability in different areas of both hemispheres in the chronic stroke patients and consequently on the motor performance of the affected upper limb.
- Bilateral or unilateral upper limb training does not have an immediate or long term significant effect on either the motor performance of the affected upper limb or the neural plasticity in the chronic stroke patients.

Delimitations

This study was delimited to:

- Forty five male patients with chronic stroke selected from the Outpatient Clinic of Kaser El Aini, Teaching Hospital, Cairo University and from the Out-Patient Clinic, Faculty of Physical Therapy, Cairo University and El Haram hospital.
- All the patients had experienced single stroke for at least twelve months but not exceeded for twenty four months.
- The patients were assigned randomly into three equal groups. The first group(G1) treated by unilateral arm training while the second group(G2) treated by bilateral weighted arm training with weight on the non affected arm and the third group(G3) treated by bilateral arm training without weight on the non affected arm.
- Fugle-Meyer Upper Extremity Motor Performance scale and Wolf Motor Function scale were used to assess the upper limb motor performance and the time of motor performance of each patient.

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- A quantitative mapping Electroencephalogram of the brain was done to detect the brain excitability in different areas of both hemispheres.

Limitations

An effort was made to minimize the effect of the possible limitations which are:

- The psychophysiological status of the patients; all the patients were interested and motivated during the sessions or the training course.
- The transportation of all patients from the Outpatient Clinic ,Faculty of Physical Therapy, Cairo University and El Harm hospital to Kaser El Aini, Teaching Hospital, Cairo University was comfortable and without any effort or extra load on the patient as much as possible.
- Each patient was assessed by the quantitative Electroencephalogram lab at Kaser El Aini, Teaching Hospital, Cairo University, at a time suitable for each patient and without any list of waiting as much as possible.

Basic assumption

- All the patients followed the instructions and the training program especially at home.
- The sample of this study represented all the chronic stroke patients.
- All other factors which may influence the outcome such as noise, distraction.....etc during the assessment and training course were controlled.
- All risk factors of stroke would be controlled to avoid any recurrent stroke or instability of their medical state like blood pressure, glucose and cholesterol level that was achieved by contact with their physicians.

Definition of Terms

Stroke (brain attack or a Cerebro-Vascular Accident (CVA))

It is sudden death of brain cells in a localized area due to inadequate or interruption of blood flow to the brain. It leads to “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.”(Woodruff et al., 2011).

Neural plasticity or Neuroplasticity

It is the capacity for brain reorganization or development of new functional connections in response to the learning and experience. This intrinsic property of the brain helps the nervous system to escape the restrictions of its own genome and adapt to environmental pressures, physiologic changes, and experiences (Stein and Stuart, 2003; Pascual-Leone et al., 2005; Meyer et al., 2014).

The task specific training

It is the training of using a task which is meaningful to the patient and involves repetition and practice (Langhammer and Stanghelle, 2000).

Inter-rater reliability

It is the stability of the data obtained by two or more evaluators from the same measurement (Pereira et al., 2011).

Necrosis

It is the death of brain tissue when there is not enough blood flowing and is not reversible. Necrosis produces an explosion of cell contents accompanied by inflammation and immune activation (Fujita and Ueda, 2007).

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Apoptosis

It is the physiological response to the damaging influences of any brain cell not working that requires sufficient maintenance of homeostasis to allow execution of the pathway (**Fujita and Ueda, 2007**).

Ischemic Penumbra (IP)

It is the core of infarction that occurs within an hour of hypoxic- ischemic insult and surrounded by an oligemic zone. It is subjected to a wave of deleterious metabolic processes propagated from the core to the neighboring tissue, including excitotoxicity, spreading depression, oxidative stress, and inflammatory response, which lead to the expansion of the ischemic core and the subsequent worsening clinical outcome (**Lin et al., 2010 ; Ramos-Cabrer et al.,2011**).

Lateralization of cerebral cortex

It is the tendency for certain processes to be more highly developed on one side of the brain than the other, such as development of spatial and musical thoughts in the right hemisphere and verbal and logical processes in the left hemisphere in most persons (**Dreosti et al.,2014**).

Mirror neurons

Are classes of neurons in the ventral pre-motor cortex and inferior parietal lobule that respond during the execution as well as the observation of goal-directed motor tasks (**Antonino, 2013**).

Sensory Integration

It is the ability to receive, organize and interpret sensory input from multiple systems in order to act on or within the environment (**Stein and Rowland, 2011**).

Review of literatures

In this chapter the review of literatures discussed under the following items:

1. Pathophysiology of human ischemic stroke.
2. Neural Plasticity.
3. The lateralized organization of motor functions in the cerebral cortices.
4. Influence of bilateral and unilateral arm training on the chronic stroke patients.
5. Influence of Sensory feedback and adding weight on the chronic stroke patients.
6. Neural plasticity and task-specific training.
7. Spectral analysis of mapping EEG (QEEG) and measurement of brain plasticity in stroke patients.
8. Clinical scales of measuring post stroke impairment.

Pathophysiology of human ischemic stroke

Stroke (brain attack or a cerebrovascular accident (CVA) is the sudden death of brain cells in a localized area due to inadequate or interruption of blood flow to the brain. Brain cells quickly die after diminishing blood flow in the brain as a result of decrease oxygen and nutrients supply to the brain cells and increase in the waste products. Stroke involves pathogenically a heterogeneous group of processes. Vessel occlusions (ischemic stroke) account for 85% of all strokes. Primary intracerebral bleeding (hemorrhagic stroke) accounts for the remainder. Embolisms cause approximately 75% of all cerebral vessel occlusions. They are the most frequent cause of focally-obstructed blood flow within the brain. Depending on the affected region of the brain, a stroke may cause paralysis, speech impairment, loss of memory and reasoning ability, coma, or death (**Woodruff et al., 2011**).

The brain is particularly vulnerable to ischemia. Complete interruption of blood flow to the brain for only five minutes triggers the death of susceptible neurons in several brain regions. Ischemia of 20–40 minutes causes death of cardiac myocytes or kidney cells. The prominent vulnerability of brain tissue to ischemic damage reflects its high metabolic rate. The human brain represents only about 2.5% of body weight but it accounts 25% of basal metabolism. The central neurons have a near-exclusive dependence on glucose as an energy substrate. Brain stores of glucose or glycogen are limited. Different brain regions have varying thresholds for ischemic cell damage. White matter is more flexible than gray matter. Certain neurons of brain are more vulnerable to ischemia as the hippocampus and pyramidal neurons. Dentate granule neurons, on other hand, are more resistant (**Lee et al., 2000; Howells et al., 2010**).

The pathophysiology of stroke is complex. It involves numerous processes, including: energy failure, loss of cell ion homeostasis, acidosis, increased intracellular calcium levels,

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excitotoxicity, free radical-mediated toxicity, generation of arachidonic acid products, cytokine-mediated cytotoxicity, complement activation, disruption of the blood-brain barrier (BBB), activation of glial cells, and infiltration of leukocytes (**fig.1**). These processes are interrelated and co-ordinated events. They can lead to ischemic necrosis in the severely affected ischemic-core regions. Within a few minutes of a cerebral ischemia, the core of brain tissue exposed to the most dramatic blood flow reduction and subsequently undergoes necrotic cell death (**Woodruff et al., 2011**).

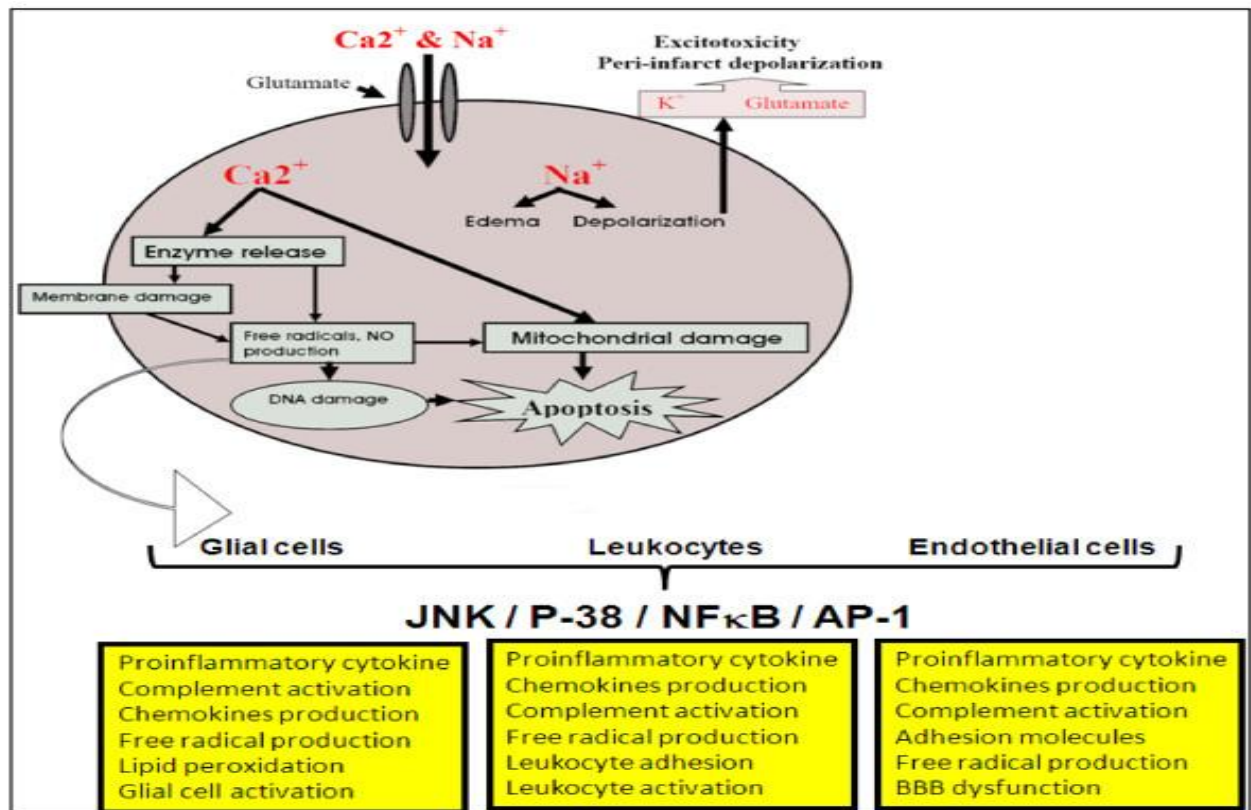


Fig.(1):Major cellular patho-physiological mechanisms of ischemic stroke

(Woodruff et al., 2011).

A significant portion of ischemia-induced neuronal damage is mediated by excessive accumulation of excitatory amino acids. This leads to increase the toxic in intracellular calcium. This is an intrinsic defensive response to protect against ischemia by activating a reaction to severe cell stress. An increase in intracellular calcium activates multiple signaling pathways leading to cell death. After reduction or termination of cerebral blood flow, energy dependent cellular pumps fail due to a fall in glucose dependent ATP generation. The flow of numerous ionic species into the cell results in cellular swelling through osmosis and cellular depolarization. Calcium ions (Ca^{2+}) enter the cell through voltage- dependent and ligand-gated ion channels, resulting in activation of a number of proteases, kinases, lipases, and endonucleases. This is

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triggering the intrinsic apoptotic pathway and ending in cell death. Glutamate is the major excitatory neurotransmitter in the brain. It accumulates in the extracellular space following ischemia, and activates its receptors. Glutamate receptor activation induces alterations in the concentration of intracellular ions, most notably Ca^{2+} and sodium ions (Na^{+})(**fig.1**) (**Mehta et al., 2007**).

Increased levels of intracellular messenger Ca^{2+} activate proteases, lipases and endonucleases. Free radicals are generated and damage membranes, mitochondria and DNA. This is in turn triggering cell death. It induces the formation of inflammatory mediators which induce JNK, p-38, $\text{NF}\kappa\text{B}$ and AP-1. All these substances activate in glial cells, endothelial cells, and infiltrating leukocytes. This culminates in pro-inflammatory cytokine and chemokine secretion. That leads to invasion of leukocytes via up-regulation of endothelial adhesion molecules. The end result is that brain ischemia is due to oxidative stress, Blood Brain Barrier (BBB) dysfunction, Leukocyte infiltration, Lipid peroxidation, inflammation and Glutamate excitotoxicity (**Mehta et al., 2007**).

Necrosis is characterized by initial cellular and organelle swelling, subsequent disruption of nuclear, organelle, and plasma membranes, disintegration of nuclear structure and cytoplasmic organelles with extrusion of cell contents into the extracellular space. The necrotic core is surrounded by a zone of less severely affected tissue. This is rendered functionally silent by reduced blood flow but remains metabolically active. This border region is known as the “ischemic penumbra”. Ischemic penumbra may comprise as much as half the total lesion volume during the initial stages of ischemia. It represents the region in which there is opportunity for salvage via post stroke therapy. Less severe ischemia, in the penumbra region of a focal ischemic infarct, evolves more slowly, and depends on the activation of specific genes and may ultimately result in apoptosis (**Fujita and Ueda, 2007**).

Ischemic penumbra may comprise as much as half the total lesion volume during the initial stages of ischemia. Many neurons in the ischemic penumbra or peri- infarct zone may undergo apoptosis after several hours or days. They are potentially recoverable for some time after the onset of stroke. Apoptosis, opposite to necrosis, appears to be a relatively orderly process of energy-dependent programmed cell death to dispose of redundant cells. Cells undergoing apoptosis are dismantled from within in an organized way that minimizes damage and disruption to neighboring cells. There are two general pathways for activation of apoptosis: the intrinsic and extrinsic pathways (**fig.2**). Apoptotic signaling cascades after cerebral ischemia can be initiated by internal events (ie, “Intrinsic Pathway”) involving the disruption of

mitochondria and the release of the cytochrome C. This leads to the downstream activation of caspases. Cell surface receptors can be activated by specific ligands that bind to “death receptors” (ie, “Extrinsic Pathway”) (Lin et al., 2010).

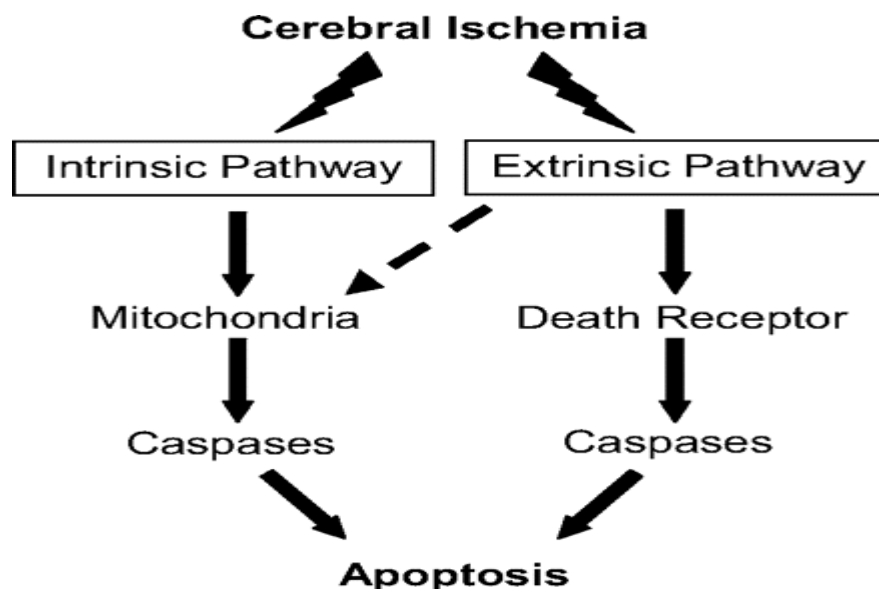


Fig.(2): Mechanism of apoptosis (Lin et al., 2010)

The brain’s inflammatory responses to post ischemia are characterized by a rapid activation of resident cells. These cells are mainly microglial cells, followed by the infiltration of circulating inflammatory cells, including granulocytes (neutrophils), T cells, monocyte/macrophages, and other cells in the ischemic brain region. In the acute phase (minutes to hours) of ischemic stroke proinflammatory mediators (cytokines and chemokines) are released rapidly from injured tissue. In the subacute phase (hours to days), infiltrating leukocytes release cytokines and chemokines, especially excessive induction/activation of MMP (mainly MMP-9). This MMP-9 amplifies the brain-inflammatory responses further by causing more extensive activation of resident cells and infiltration of leukocytes. This leads to disruption of the blood brain barrier (BBB), brain edema, neuronal death, and hemorrhagic transformation. Most of these proinflammatory factors have a dual role at early and late stages of stroke. Regardless of the cellular origin, MMP-9 has been shown to affect early ischemic brain damage detrimentally but promote brain regeneration and neurovascular remodeling in the later repair phase (fig.3) (Rong et al., 2010).

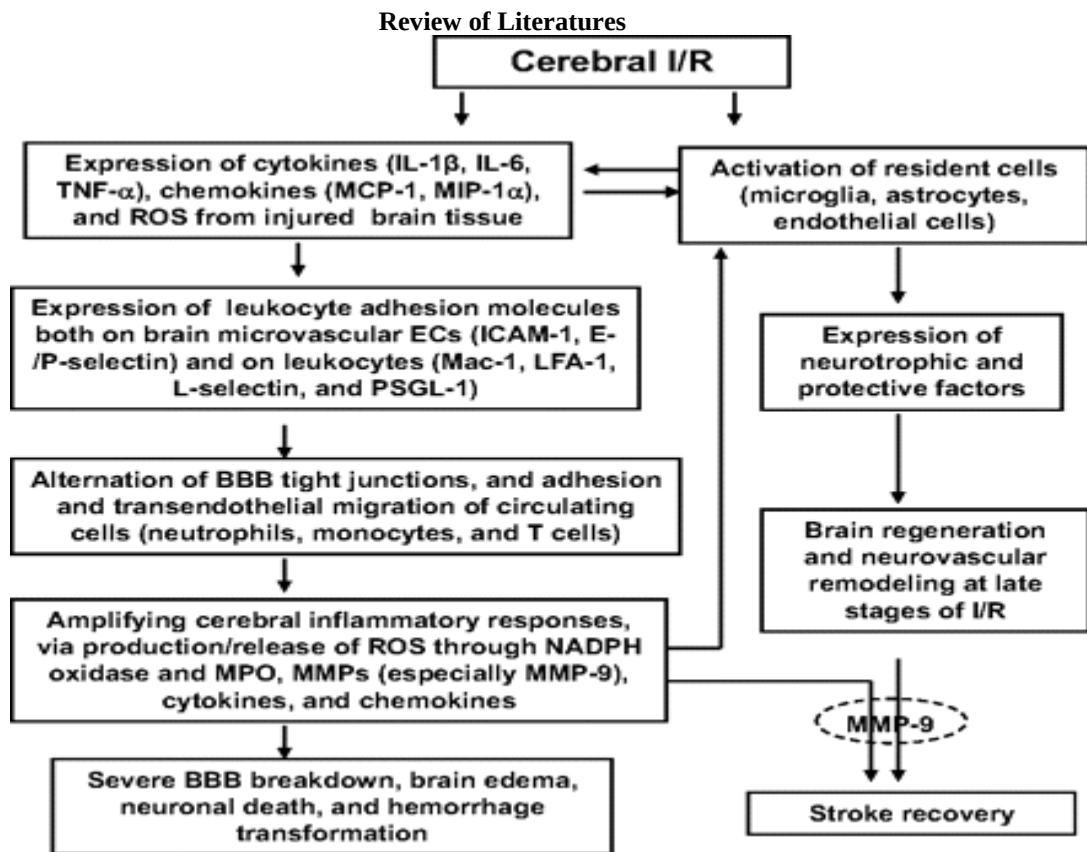


Fig.(3): Potential inflammatory pathways that respond to cerebral I/R

(induced / reperfusion)) (Rong et al., 2010)

Neural plasticity

Post stroke brain repair revealed the complexity of the processes initiated by the lesion in the brain. These processes include molecular, cellular, and systems mechanisms that take place in peri-lesional, as well as remote brain areas. Early after stroke, focal cortical injury induces highly coordinated temporally and spatially expression/suppression of genes coding for growth stimulating and growth inhibiting proteins. Intensive local rewiring takes place: stimulation of neurite outgrowth, axonal sprouting and formation of new synapses. Peri- infarct neurons become hyper excitable, and glutamate receptors are up regulated, while GABA-ergic receptors are down regulated. These processes may underlie the brains self-repair mechanisms. Undamaged neurons surrounding the infarcted area may also play significant roles in subsequent functional recovery **(Koganemaru et al.,2010)**.

Neural plasticity is still one of the most challenging questions in neuroscience. According to the theories of neuroplasticity, thinking and learning change both the brain's physical structure and functional organization. Neurogenesis, programmed cell death, and activity-dependent synaptic plasticity are the main mechanisms of brain plasticity. Repetitive stimulation of synapses causes long-term potentiation or long-term depression of

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neurotransmission. These changes are associated with physical changes in dendritic spines and neuronal circuits that eventually influence behavior. These mechanisms are important contributors to the developing brain's ability to acquire new information, adapt to the rapidly changing environment and recover from injury (**Johnston, 2009**).

Spontaneous recovery may be due to resolution of edema and possibly recovery of tissue function in tissues that were ischemic but not destroyed. This aspect of recovery occurs within a few days. Brain plasticity is responsible for recovery beyond this acute period. The brain is not only capable of plastic changes, but is constantly changing. Plasticity is responsible for learning. Learning implies a change of the brain. As long as the brain can learn, it can change. Similar changes are likely to be helpful in recovery from injury. The cellular mechanisms which are responsible for plasticity in humans are under active investigation. The first process of plasticity is a change in the balance of excitation and inhibition (**Bowdena et al., 2013**).

The balance of excitation and inhibition process depends on neurons or neural pathways. Anatomical connections of these neurons or neural pathways have a larger region than their functional influence. Some zones do not change by tonic inhibition. If the inhibition is removed, the region is quickly increased or unmasked in a process often called unmasking. The second and faster process of plasticity is strengthening or weakening of the existing synapses by processes of long-term potentiation (LTP) or long-term depression (LTD). A change in neuronal membrane excitability is the third process. The fourth process is anatomical changes, which need a longer period of time. Specific anatomical changes include sprouting of new axon terminals and formation of new synapses. These processes operate in different time periods and are not mutually exclusive; indeed, one can be followed by another serially and this is likely to occur (**Bowdena et al., 2013**).

The capacity of the brain depends mainly on the number of synaptic connections not on the number of neurons. Synaptic connections develop as a result of genetic programming and a lifetime of experience. The capacity for cortical reorganization or development of new functional connections in response to learning and experience is referred to as "plasticity". Plasticity allows the recovery of the function lost after losing the neurons and associated functional connections. Learning differs completely from development. Development is the change in an organism as a result of growth, maturation, and/or experience. The acquisition of a skill or gain of knowledge through study, instruction, and/or experience is referred to as learning. The individuals learn skills after hours, days, and months of practice while developmental change occurs over weeks, months, and years. Plasticity that emerges from

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typical development represents the neural change that is following the phylogenetic norm; in contrast, plasticity that emerges following learning represents the neural changes associated with experience that is specific to the individual (Cauraugh and Summers, 2005; Meyer et al., 2014).

Both development and learning mechanisms induce neural and behavioral plasticity (fig.4). Experience-expectant mechanisms are needed for development. Learning on other hand, needs experience-dependent. Experience-expectant mechanisms utilize environmental information. Experience-dependent mechanisms, in contrast, are sensitive to the individual experiences of specific inputs. Experience-expectant mechanisms share common developmental time points across individuals (e.g. visual experience is expected at roughly the same developmental time point, shortly after birth). Experience-dependent mechanisms are differ in developmental timing among individuals (Smith and Thelan, 2003).

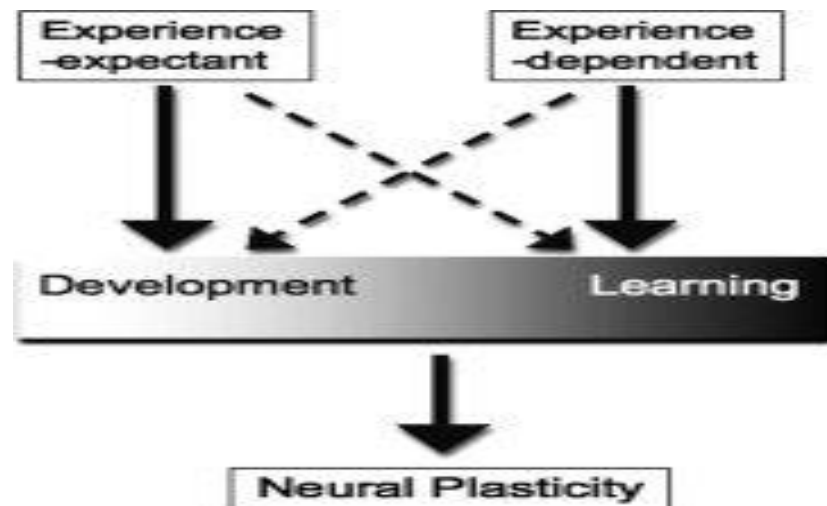


Fig.(4): Development and learning are simultaneously influence neural plasticity

(Smith, Thelan, 2003)

Structural changes, as measured by MRI, typically refer influence of experience on anatomical changes. This change is indexed as volumetric differences in morphometry of particular brain region. Functional changes refer to differences in neural activation patterns following a particular experience. The functional methodology measures the changes in blood oxygenation in the brain. These changes reflect the brain activity. Structural and functional changes are not synonymous with each other. Functional remapping may observe without any significant structural changes. Morphometric changes in a particular brain region do not always confer functional and/or behavioral changes (Logothetis et al., 2001).

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Synaptic changes affect the strength of local associations between neurons that contribute effectively toward task processing. This phenomenon results in selective pruning of synapses that are overproduced early in development. Extra synapses are lost by time and the final system consists of synapses that were selectively retained. This dual influence directly stems from the contribution of experience-expectant and experience-dependent mechanisms. Experience-expectant mechanisms encourage the elimination of unnecessary synapses or neural units (brain waves frequency decreases). Experience-dependent mechanisms guide activity-dependent creation and strengthening of synapses based on the individual organism's experience and needs (brain waves frequency increases). At the synaptic level, this phenomenon is called metaplasticity, and refers to the notion that properties of synaptic plasticity can change as a function of previous plasticity and previous activation of synapses (**Logothetis et al., 2001 ; Draganski and May, 2008**).

Increasing cortical grey matter results from a complex array of morphological changes. This is including synaptic events such as the formation of new connections by dendritic spine growth and alterations in the strength of existing connections. In animals exposed to enriched environments, increased size of the soma and nucleus of neurons, glia and capillary dimensions have also been shown to influence cortical morphology. Further mechanisms linked to training and experience-related plasticity include changes in the synaptic contacts known to be the morphological substrates of long-term potentiation and long-term depression, synaptic pruning, changes in gene expression, protein synthesis and dendritic density (**Carey et al., 2005**).

Proton MR spectroscopy (1H-MRS) provides insights into metabolic events involved in poststroke recovery. Low ipsilesional N-acetylaspartate (NAA), specifically, a marker of neuronal integrity, is related to cortical dysfunction. It is also correlated to poor behavioral outcome and possibly diaschisis. Other 1H-MRS-visible metabolites like, myo-inositol (mI) provides insights into the role of glia in plastic brain changes or into nonsynaptic mechanisms underlying plasticity. Glutamate/Glutamine (Glx) reflects the neuronal–glial neurotransmission system. It might provide further insights into synaptic mechanisms underlying plasticity. The metabolite concentrations would be related to arm/hand motor abilities (**Giroud and Beley, 2004**).

There are positive relationships between ipsilesional NAA and clinical severity and between contralesional NAA and stroke duration. This provides support for NAA as a marker of poststroke reorganization in both injured and uninjured hemispheres. Myo-inositol was significantly increased across the ipsilesional and contralesional M1 compared with control