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NEUROPHYSIOLOGICAL ASPECTS OF PLASTICITY OF THE BRAIN

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The concept of Neuronal plasticity has been extensively used to deal with the enduring changes associated with brain's capacity to be shaped or moldered by experience, the capacity to learn and remember and the ability to reorganize and recover after injury. Synapse formation during development is thought to be depended upon both the genetic and environmental influences. This initial stages of synapse formation occurs independent of experience. Experience dependent refinement occurs during the critical period. A common view held that, after this critical period of fine turning, the resulting configuration of synaptic connections remained unaltered throughout the life time of the animal. However, research over the last two decades has provided evidence for extensive experience dependent plasticity in the adult brain[1]. One of the early demonstrations of adult cortical plasticity in the primate somatosensory cortex has been carried out by Merzenich and co-workers[2] in 1978. A wide range of neuronal response reconstruction studies conducted in animals and humans have shown that cortex reorganizes its effective local connections and responses following peripheral, central alterations of inputs and in response to behaviour[3;4] . Subsequent studies have shown that environmental enrichment , standard learning tasks help to improve brain functions and promote brain plasticity in adults[5;6].

Understanding the neuronal basis of neural plasticity has been the goal of considerable research. The "Hebbian” theory attempts to provide much insight into the mechanisms of neuronal plasticity. It postulates that the temporal correlation of pre-and postsynaptic activity leads to synaptic strengthening, whereas lack of this correlation results in synaptic weakening[7] . After a decade, theories of structural plasticity began to emerge and later studies demonstrated the experience dependent structural changes in the presynaptic and post synaptic elements. The stage has been now set to accept the concept of neurogenesis in the adult neural system. Neuronal plasticity may be associated with i) activity dependent modification of the efficacy of existing synapses leading to long-term potentiation (LTP) or long-term depression (LTD), ii) morphological changes leading to enhanced dendritic branching and axon collaterals and iii) synaptogenesis leading to generation of new synaptic contacts[8-11] iv) neurogenesis leading to the incorporation of new neurons to influence subsequent behaviors.

It is widely believed that LTP holds the key for understanding how memories are formed in the brain. LTP is a long lasting enhancement of synaptic effectiveness that follows a brief, high frequency electrical stimulation in the hippocampus where it was first documented by Bliss and Lomo[12] and in other brain regions such as neocortex, brain stem and amygdala. Recent evidences suggest that induction of LTP may require, in addition to postsynaptic calcium entry, activation of metabotropic glutamate receptors and the generation of diffusible intercellular messengers. A new form of synaptic plasticity homosynaptic long- term depression (LTD) has also recently been documented, which like LTP requires $Ca2^+$ entry through NMDA receptors. Studies suggest that LTD is a reversal of LTP, and vice versa, and the mechanisms of LTP and LTD may converge at levels of specific phosphoproteins[8].

Some of the most detailed studies of experience dependent plasticity have been performed in the rodent barrel cortex. Manipulations of the sensory inputs such as, clipping the whiskers can change the receptive fields of cortical neurons. Robust experience dependent plasticity has been observed within 24 hrs of whisker clipping[13]. These models demonstrates the cellular basis of this experience dependent plasticity due to modifications of existing synapses such as long-term potentiation and depression[3].

There was little evidence for rapid synaptogenesis in the adult brain in response to sensory stimulation. Recent electron microscopic studies provide evidence that the adult cortex generates new synapses in response to sensory activity within 24 hr of sensory stimulation. Knott et al[4] studied the effects of stimulating a single whisker on synapses in the barrel cortex of mice. Remarkably, after this relatively brief period of stimulation, they observed a significant increase in both synapse and spine density specifically in the barrel corresponding to the stimulated whisker. Their study suggest that new synapses form predominantly on spines, either through addition of a new synapse on the preexisting spine or by the growth of new spines. Whisker stimulation resulted in a transient increase in excitatory synapses; however, there was an absolute increase in total inhibitory synaptic density and a shift of inhibitory synapses from shaft to spines. This enhanced inhibitory synaptic density could account for the powerful homeostatic mechanisms that keep the neuronal activity in a reasonable operating range, may be to preserve the network stability[15]. The observed increase in inhibition may act to reduce the excitation of layer IV neurons in response to sensory stimuli.

Activity dependent synaptogenesis is thought to be mediated by gene expression and protein translation. In adult animals, whisker stimulation causes upregulation of immediate early-genes[16] and experience-dependent plasticity paradigms cause CRE-mediated gene expression such as brain derived neurotrophic factor (BDNF)[17]. Activity dependent up regulation of BDNF leads to spine growth and recruitment of new synapses and proposed to enhance dendritic morphogenesis. Enhanced synaptic density and changes in expression of Fos protein associated with a complex motor learning task has been reported[18]. It is generally assumed that the global nature of the motor learning task may demand the integration of a variety of inputs. Similarly it is assumed that Fos proteins play a role in the memory process[19]. Disrupting the functions of cAMP element response binding (CREB) protein which induce the transcription of c-fos gene has been reported to cause learning impairment in drosophila[20]. FOS may act to promote the transcription of various proteins (necessary for changes in neuronal structure and function) such as nerve growth factor, deregulate cytoskeletal proteins to promote morphological transformation. It is most likely involved in cellular process associated with cell function that may be up regulated during periods of plastic change. Animals lacking functional c-fos gene are impaired on some learning task and may be attributed to a gross behavioral impairment rather than specific learning deficit [21].

The molecular mechanisms involved in neuronal plasticity have been a topic of intensive research in recent years. The gene knock out technology further enhanced the understanding of the role of genes and proteins in synaptic plasticity [22;23]. The occurrence of experience dependent, CaMK II dependent LTP phenomenon has been reported in the hippocampus[9] and in many cortical areas[3]. In contrast, CaMK-II gene knock out mice fails to elicit both the behavioral plasticity and generate the potentiation phenomenon.

Physiological examination of mouse knockouts has demonstrated roles for CaMK II and CREB in activity dependent barrel cortex plasticity[24].

There is an increasing evidence that neurotrophins (NTs) are involved in processes of neuronal plasticity besides their well established action in regulating the survival, differentiation and maintenance of functions of specific populations of neurons. The NTs and their presynaptic Trk receptor activation contribute to the activity dependent plasticity by various means; through modifications of pre synaptic machinery locally, regulation of synaptic protein levels and transcriptional regulations[10;25]. There is increased evidence of neurotrophins and their receptor signaling in the production of LTP and activity-dependent plasticity associated with learning. BDNF expression and TrkB signaling has been associated with dendritic and synaptic restructuring by means of regulating spine dynamics, functional maturation of presynaptic terminals, dendritic growth, triggering AMPA receptor proteins and in activity dependent conversion of silent synapses into functional ones[10]. The cascade of cellular events associated with the changes in dendritic structure is a very complex process involving synthesis, targeting and transport of essential proteins. A combination of local regulation of trophic factor receptor activation and protein synthesis could be the principle mechanisms leading to the structural plasticity. Recent advances in imaging technology permits the real time observation of dendritic spines , and therefore can detect the dynamic structural changes associated with synaptic plasticity[26]. Sensory deprivation by unilateral whisker trimming for a short duration decreased the motility of dendritic spines in deprived regions and degradation in the tuning of layer II and III receptive fields. These studies suggest that sensory experience drives structural plasticity in dendrites which may underlie reorganization of neural circuits during plasticity. Although short term changes in synaptic strength are attributed to changes in existing synapses, structural changes represent one of the key feature of the long-term memory process, either through formation or elimination of synapses[27]. Support for structural dynamics including synapse formation and elimination has been demonstrated following sensory experience in adult barrel cortex[18], learning[27] and in other plasticity evoking paradigms[10].

Recent research has shown the existence of neural stem cells in the sub ventricular zone, olfactory bulb and in the dentate gyrus of hippocampus[28, 29] which give rise to new neurons and glial cells. It is postulated that the new cells undergo differentiation to be incorporated into the existing functional network and allow a strategic increase in network complexity may be to accommodate the continued modulation of input pathways. Thus it appears that behaviors can induce structural changes and changes in structure can subsequently change or at least affect subsequent behavior.

Activity dependent synaptic plasticity has been implicated in a variety of physiologically and behaviorally induced changes in neuronal organization both during development and adulthood. Although extensive information is available about the mechanisms of synaptic plasticity in the adult mammalian brain, a coherent understanding has yet to be emerged.

> *“Brain- an enchanting loom”;*
> *the threads of the loom can be broken either by internal perturbations like lesion or by external perturbations like learning. New threads then form, branch out and give different pattern - always shifting but a meaningful pattern.*
>
> **Sir Charles Sherrington (1857-1952)**

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