CHAPTER 2

REVIEW OF RELATED LITERATURES

In the normal development of the vertebrate nervous system, a remarkably larger number of neurons are normally lost during a period. However, in vertebrates the survival of neurons during development is critically dependent on interactions between the neuron and its target.

Studies by several investigators [15,16,17] showed that transplanting an additional limb bud could increase the number of sensory and motor neurons in the spinal cord of amphibian or chick embryos. Conversely, removing the normal target could decrease the number of neurons (Figure 3). The difference in the final number of neurons, demonstrated in these experiments, was thought to result from an effect of the target on the proliferation and differentiation of neuron.

Bueker demonstrated that the mouse sarcoma tissue could evoke extensive innervation of sensory fibers to the tumor. He also observed that dorsal root ganglia near the size of tumor implantation were significantly larger than the corresponding ganglia on the opposite side of the spinal cord. It was without effect on motor neurons.[18]

These experiments were extended by Levi-Montalcini and Hamburger who noted a dramatic increase in the size of sympathetic and sensory ganglia in the vicinity of the sarcoma implants.[19,20] Further studies showed that the effect of the sarcoma was caused by a diffusible factor after transplantation of tumors onto the chorioallantois, which were therefore only in communication with the embryo via circulation. They later developed quantitatives in vitro assays to measure the effect of the tumor tissue on the survival and outgrowth of axons from sensory and sympathetic ganglia. The diffusible molecule was then purified by Cohen and named nerve growth factor (NGF).[21]

Only a few populations of neurons, including sympathetic and some sensory neurons, are NGF dependent. The existence of these non-NGF neurotrophic activities

led to efforts to purify other survival factor during the 1960s, 1970s, and 1980s. Unlike NGF, which was purified and named brain derived nerve growth factor (BDNF), neurotrophins 3 to 6 (NT-3 to NT-6). It was called neurotrophins. Neurotrophins signal via the high affinity tyrosine kinase receptor (trk); the participation p75NGF receptor (p75NGFR) in neurotrophin signally remains controversial.[22,23,24]

It believed that target tissues release only limited amount of the trophic factor (e.g. NGF) which is not sufficient for the entire population of neurons initially generated. This causes the death of between 50 to 80 percent of neuronal originally generated.
It should be stressed that the axon, through its terminal synaptic ramifications, plays a key role in the retrograde transport of the neurotrophic factors from the target tissues. Thus, axonal transection or axotomy, particular during development, causes rapid cell death. NGF was shown to act in this manner by supporting the survival of axotomised sensory.[25,26,27]

Stanley Cohen proposed that both lymphocyte derived and non-lymphocyte-derived chemotactic and migration inhibitory factors be grouped into families of cytokines. Many cytokine were named according to the particular biological activity that was the basis of their isolation, only to be later rediscovered or renamed as important mediators of other physiological processes. LIF is a member of broader family of neuropoietic family, including ciliary neurotrophic factor (CNTF), oncostatin M, and cardiotrophin-1, that share a common three-dimensional structure and receptor subunits.[28,29] The LIF receptor is composed of two different transmembrane subunits, gp130 and LIFRβ. When LIF binds, the two subunits associate Janus kinases (JAK) and the subsequent recruitment of signal transducers and activators of transcription (STAT) proteins. The gp130-associated kinases Jak-1, Jak-2, Jak-3 and Tyk-2 become phosphorylated. These phosphotyrosine moieties act as docks for the STAT to the nucleus, where they regulate the transcription of target genes (Figure 4).

Leukemia inhibitory factor is a multifunctional polypeptide cytokine/growth factor. It has a number of actions in the immune system and other nonneuronal tissues. Although very well characterized in vitro, much less is known about the effect of LIF on nerves in vivo. Within the central and nervous system and peripheral nervous tissue, LIF has been shown to affect proliferation, differentiation and survival of neuronal and nonneuronal cells. LIF promotes the survival of cultured dorsal root ganglion and cholinergic spinal motor neurons in vitro and promotes similar features in axotomized neonatal rats.[30]

The importance of LIF in neural development and function is strengthened by several studies. They showed that LIF can produce proliferation and survival of sensory neuron during continues embryogenesis into neonate life and effect of LIF can promote the innervate of sensory neuron to target tissue.[31]

In vivo studies have demonstrated that leukemia inhibitory factor rescues motor and sensory neurons in neonatal rat. This trophic agent has been shown to rescue sensory and motor neurons in neonatal rat. Three days after sciatic nerve transection; there was 40% cell loss on the lesioned side of the sensory neuron. By 7 days, there was a 50% loss of sensory neuron. In motor neurons, resulted in the loss of 38% after 3 days and 55% after 7 days. When the axotomized nerves were treated with LIF, loss in both neurons was significantly rescued to 20-40% of axotomized neurons. [32,33]

Study of adult rats have shown a cell loss of 23% in the L5 dorsal root ganglia 60 days after sciatic nerve axotomy only.[34] Contrarily, in the same period of time, after sciatic nerve axotomy with ligation, the sensory neuron loss was 35%. [35,36]

The present studies examined the time course of sensory and motor neuron loss after axotomy only, compared with axotomy with ligation. The study investigated the ability of LIF to prevent the loss of sensory and motor neuron after median and ulnar nerve axotomy in young adult rats.

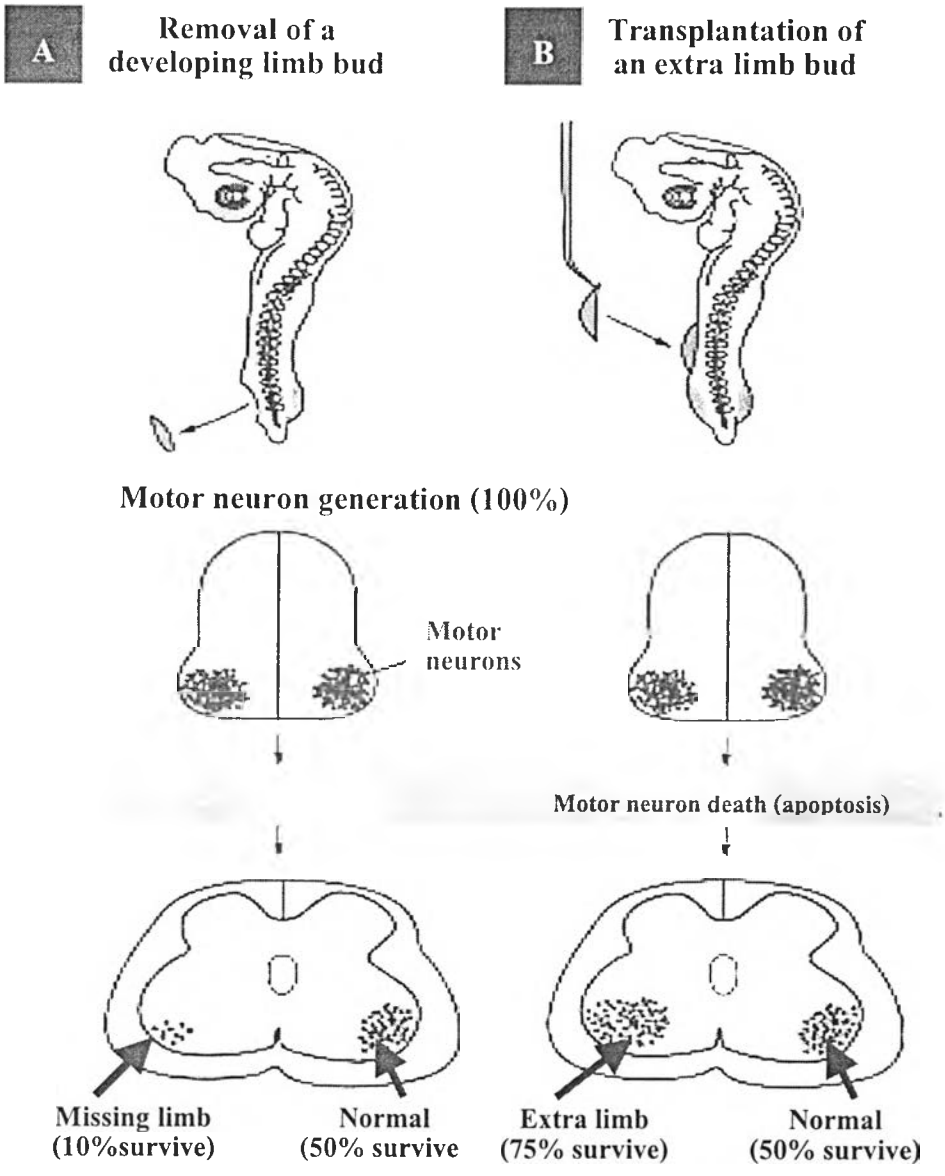
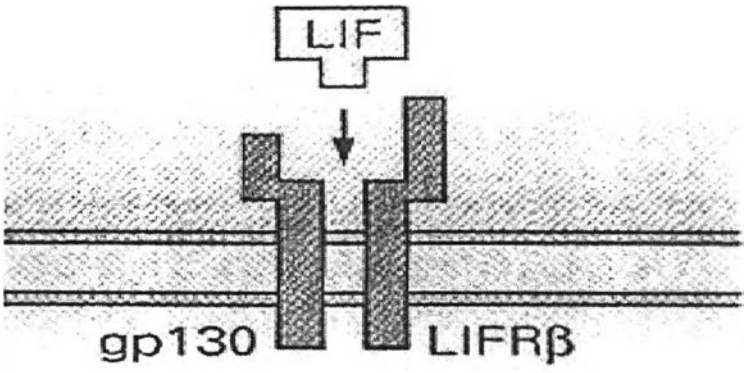
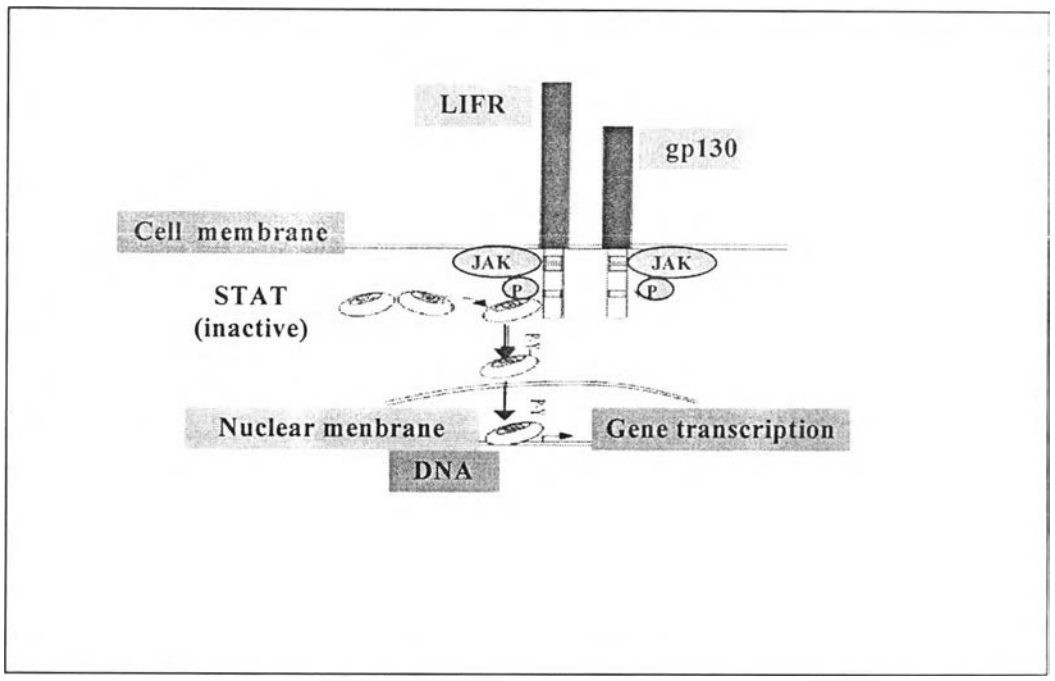


Figure 3 Changing the size or activity of the muscle target controls the survival of motor neurons.[37] *(A)*, Removing a developing limb results in marked decrease in the number of motor neurons. Limb bud amputation is performed in a chick embryo at about 2.5 days. Although motor neurons are generated in normal numbers, later in development few motor neurons remain on the side of the spinal cord on the side of the missing limb. The number of motor neurons on contralateral side is about 50% of the number generated originally. *(B)*, Increasing the size of the limb target reduces the extent of naturally occurring neuronal death during development. Transplantation of an extra limb bud prior to the normal period of cell death in a chick embryo results in an increased number of limb motor neurons on the side with additional target tissue.



(A)



(B)

Figure 4 *(A)*, LIF transduce signals via common receptor subunits, gp130 and LIFRβ. *(B)*, Signal transduction through the LIF receptor. Ligand occupancy of the LIF receptor promotes heterodimerization with pg130. Associated JAKs become activated and phosphorylate specific cytoplasmic motifs of gp130, which as a consequence create docking sites for STAT factors. In turn, STATs also become phosphorylated, form homo- or heterodimers and translocate to the nucleus, where they regulate gene transcription. STATs are also substrates for serine/ threonine kinase.[39]