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Neuro-Protection after Traumatic Brain Injury: Novel Strategies.

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Abstract: *Traumatic brain injuries (TBI) are increasing cause of functional disability which requires aggressive researches on neuroprotective agents to prevent or rectify the consequences of organic brain damage and to enhance rehabilitation. Many of the drugs which proves beneficial in preclinical studies failed to translate into clinical practice, hence the search for the ideal neuroprotective drug continues. Since the pathophysiology of TBI is highly complex and variable with multiple factors playing their roles simultaneously, it's a very tiring job to find out a novel agent. When we try to alter one of the patho-physiological aspect of TBI, it affects many targets at a time, in the same manner as the waves affect the multiple points when we throw an object into pond. As the many aspects of the TBI are still obscured, it will be of great difficulty to search a suitable target which has got pronounced effect on TBI. The failure of newer molecules to fulfill its promise can also be attributed to the flaw in pre-clinical and clinical studies. Eventually the journey to have an ideal neuroprotective agent still continues.*
Key Words: *Traumatic Brain Injury, Neuro-Protection.*

I. Introduction

Traumatic brain injury (TBI), also known as acquired brain injury, head injury, or brain injury, causes substantial disability and mortality. Traumatic Brain Injury is a significant public health problem worldwide and is predicted to surpass many diseases as a major cause of death and disability by the year 2020[1]. The majority of TBI cases (60%) are a result of road traffic injuries (RTI), followed by falls (20-30%), and violence (10%)[2]. In India it is estimated nearly 1.6 million individuals will sustain TBI and seek hospital care annually[3].RTI are the leading cause of TBI in India accounting for 45-60% of TBI, and falls account for 20-30% of TBI, paralleling the findings from the Global Burden of Disease Study[4]. Traumatic brain injury causes mechanical tissue destruction which can be supposed to be the primary mechanism of brain injury that results in neuronal cell death causing cerebral edema and rise in intracranial tension contributing to impaired cerebral vasoregulation, cerebral ischemia/hypoxia and brain damage. Primary injury itself acts as trigger for secondary mechanism responsible for brain injury i.e. the neuronal cell death associated with cerebral ischemia is due to the lack of oxygen and glucose, and may involve the loss of ATP, excitotoxicity of glutamate, oxidative stress, reduced neurotrophic support, and multiple other metabolic stresses[5]. One major event taking place at the moment of TBI is the massive ionic in flux referred to as traumatic depolarization. Excitatory amino acids may play a vital role in this depolarization. This represents one of the most important mechanisms of diffuse neuronal cell dysfunction and damage associated with TBI. Cerebral edema and associated increased intracranial pressure are the major immediate consequences of TBI that contribute to most early deaths. There are at least two kinds of delayed and progressive patho-biological changes induced by TBI. One of these is axonal damage, which is not the direct consequence of traumatic tissue tearing. Rather, results from complex axolemmal or cyto-skeletal changes, or both, which lead to cyto-skeletal collapse and impairment of axoplasmic transport. The other change in traumatized brains occurs concomitantly with compromised blood brain barrier (BBB) function. Secondary damage in TBI is influenced by changes in cerebral blood flow (CBF), cerebral metabolic dysfunction and inadequate cerebral oxygenation. Excitotoxic cell damage and inflammation may lead to apoptosis[6]. Furthermore, it is also becoming clear that these secondary insults are, to a significant degree, are preventable. Since multiple derangements starts simultaneously it is essential to have effective neuroprotective therapy to prevent early brain damage. Management of head injury focuses on preventing, detecting and correcting the secondary brain injury after trauma. Duration and severity of such secondary brain damage influences the possible outcome. Unfortunately, numerous neuroprotective drugs have failed to demonstrate beneficial effects in Phase II/III clinical trials, despite

previous encouraging preclinical results[7]. However, some drugs that have been approved for use in the clinic have neuroprotective effects, and these could be used for the treatment and improvement in functional recovery in patients of traumatic brain injury.

II. Neurogenesis after TBI:

First proposed nearly a century ago, the persistence of neural stem cells and neurogenesis in the adult mammalian central nervous system (CNS) is now accepted[8]. Adult neurogenesis is found in these forebrain regions in all mammalian species examined, including humans and may serve to replace cells damaged by brain insults[9,10]. Significant self-recovery occurs following all but the most severe episodes of TBI[11]. The mechanisms underlying this remain unclear, though injury-induced neurogenesis is one compelling potential contributor to post-injury recovery[12]. The two most well studied and validated reservoirs for neural stem and progenitor cells in mammals are the SVZ of the lateral ventricles and the SGZ of the dentate gyrus[13]. Normally, the postnatal SVZ contributes progenitors to the rostral migratory stream to support ongoing olfactory neurogenesis, while the SGZ of the dentate gyrus provides new granular neurons throughout life[13,14]. Following TBI, progenitor cells in each of these areas become activated, though it is still unclear whether this activation results in stable and productive neurogenesis[12]. Stem cells from the adult brain proliferate and differentiate into neurons and glia in tissue culture with the same efficiency for neuronal differentiation as found in fetal stem cells. Recent studies have shown that they can differentiate to neurons in the adult human dentate gyrus in vivo. Injury to the hippocampus has been associated with learning and memory deficits, which are the hallmarks of TBI. Neurogenesis in this region has been implicated in learning and memory functions[15.] Despite a constant decline in NPC proliferation in the dentate gyrus from adolescence through senescence[16-18], the adult brain up-regulates proliferation to almost the same extent as the juvenile brain after TBI[19], indicating that NPCs conserve the ability to respond to proliferative signals Although neurotrophins are upregulated after TBI[20], the aging hippocampus has been reported to contain less brain-derived neurotrophic factor (BDNF) in comparison to the hippocampus of younger injured animals after kainic acid injury[21], suggesting that the neurotrophic response to injury in the hippocampus is age dependent, which may be responsible for better outcome in children and young adults.

Role of neurotrophic factors

Neurotrophic factors are endogenous proteins which have been shown to play a critical role in the normal development of neurons and appear to mediate a protective response to trauma and disease.They may also play important role in neuro plasticity. It is seen in animal studies that a particular neurotrophic factor increases survival of specific variety of neuron and it may have negligible effect on other class of neurons. During development, neurotrophins almost undoubtedly enhance cell survival by regulating the natural cell death process termed apoptosis[22]. Although the exact role of neurotrophins in neurogenesis following TBI has not been well established,but studies are going on to unlock the facts behind this mystery.

Neuroplasticity

Neuroplasticity (cortical re-mapping) refers to the ability of the human brain to change as a result of one's experience, so the brain is 'plastic' and 'malleable'. A surprising consequence of neuroplasticity is that the brain activity associated with a given function can move to a different location; this can result from normal experience and also occurs in the process of recovery from brain injury. Neuroplasticity is the fundamental issue that supports the scientific basis for treatment of acquired brain injury with goal-directed experiential therapeutic programs in the context of rehabilitation approaches to the functional consequences of the injury. The evidence for neurogenesis is mainly restricted to the hippocampus and olfactory bulb, but current research has revealed that other parts of the brain, including the cerebellum, may be involved as well[23]. Two aspects of neuronal plasticity are important for information processing: plasticity of intrinsic excitability, that is, the change in ion channel properties; and synaptic plasticity and the change in the strength of synapses between two neurons. Several mechanisms are likely to be involved in brain plasticity. Activity-dependent modification of synaptic connections and reorganization of adult cortical areas are thought to involve long-term potentiation (LTP) and long-term depression (LTD), mechanisms by which information is stored in the mammalian central nervous system[24,25]. Long-term potentiation (LTP) is a rapidly developing persistent enhancement of the postsynaptic potential response to presynaptic stimulation after a brief period of rapidly repeated stimulation of the presynaptic neuron. It may be much more prolonged and can last for days. LTD is the opposite of LTP. It resembles LTP in many ways, but it is characterized by a decrease in synaptic strength. It is produced by slower stimulation of presynaptic

neurons and is associated with a smaller rise in intracellular Ca^{2+} than occurs in LTP. It is believed to be due to dephosphorylation of AMPA receptors, decreasing their conductance and facilitating their movement away from the synaptic plasma membrane . Synaptic plasticity in cortical horizontal connections has been proposed to underlie cortical map reorganization[26-28].Glutamate, the main excitatory neurotransmitter, plays a crucial role. Cortical map reorganization in the primary somatosensory cortex can be prevented by blockade of N-methyl-D-aspartate (NMDA) receptors[29-31].g-Aminobutyric acid (GABA)-A receptor antagonists can facilitate LTP induction in neocortical synaptic systems, and the induction can be blocked by GABA-A receptor agonists[28],indicating a complex interplay between excitatory and inhibitory neurotransmitters. Transmitters released by the diffuse neuromodulatory systems originating in locus coeruleus (noradrenaline), nucleus basalis (acetylcholine), lateral tegmentum (dopamine), and raphe nuclei (serotonin) may modify the process[32-33].

The neurogenesis do occur after excitotoxic and mechanical lesions in dentate gyrus in rats[34] and must also be there in human being.Implantation of fetal neocortical cells after cortical lesions has been performed successfully in several laboratories[35]. Transplanted cells can interact with the host tissue by forming connections but also by being a source of trophic factors that can influence the surrounding tissue. Although both anatomic and functional integration with the host brain have been observed[36], improvement in behavioral tests have been noticed only when transplantation is combined with posttransplantation housing in an enriched environment[37-38].

Hippocampal neurogenesis is dependent on both genetic[39] and environmental factors[40], but the mechanisms underlying the effect of social interaction in early and adult life on hippocampal neurogenesis are largely unknown. Neurons respond differentially to specific temporal and spatial patterns of inputs. This response specificity is not always programmed into neurons; rather, it can develop as the animal interacts with the environment.Social environments can modify neurogenesis and synaptic plasticity in adult hippocampal regions, which is associated with alterations in spatial learning and memory[41],indicated by manipulating these things during rehabilitation we can improve the recovery following TBI.

Although the mechanism of neurogenesis is not clear,but it exists as indicated by recovery of learning, memory, attention etc. after few months of TBI. This may take few months to year but definitely recovery of functions do occur.

III. Pharmacological Targetting Of Various Mechanisms For Neuroprotection:

1. Free radical scavengers:

The pre-clinical studies of traumatic brain injury evaluating antioxidants and free radical scavengers have shown promising results but translation into clinical practice is still required[42,43]. There were two multicentric clinical trials evaluating Tirilazad Mesylate, 21-aminosteroid which inhibits lipid peroxidation, which resulted in no significant effects in moderately and severely injured patients[44,45]. Another clinical study in Europe evaluating the NOS inhibitor, lubeluzole, to treat TBI was stopped, mainly after the drug failed to significantly decrease mortality after ischemic stroke, despite evidence for an improvement in the outcome of surviving patients[46-47]. Edaravone was the first free radical scavenger developed as a neuroprotective drug to be used for the treatment of stroke[48.] Edaravone administration following TBI inhibited free radical mediated degeneration of neurons and apoptotic cell death around the damaged area, with improvement in cerebral dysfunction following TBI in rats[49]. Alongwith all these pharmacological effects edaravone also increased neural stem cell numbers around the area of damage following rat TBI[50]. Clinical studies are going on for testing the efficacy of it[51]. Ebselen is a mimic of GSH peroxidase which also reacts with peroxynitrite[52] and can inhibit enzymes such as lipoxygenases[53], NO synthases[54], NADPH oxidase[55], protein kinase C[56]. Ebselen protected the brain from ischemic damage in the acute stage[57]. The ceria[58] and yttria[59] nanoparticles act as direct antioxidants to limit the amount of reactive oxygen species required to kill the cells and this group of nanoparticles could be used to modulate oxidative stress in biological systems. Still research is going on with the hope to find an ideal antioxidant which will also be useful in clinical setting.

2. Neuroimmunophilins:

Cyclosporin A (CsA) an 11-member cyclic peptide is known to be potent immunosuppressant and is widely used in organ transplantation and auto-immune disorders[60,61]. In the last few years this useful compound has become of great interest to neuroscientists for their unique neuroprotective and neuroregenerative effects. This exerts its effects via immunophilins, the protein receptors for these agents. The immunophilin ligands show promise as a novel class of neuroprotective and neuroregenerative agents that have the potential to treat a variety of neurologic disorders. Cyclosporin A, at therapeutically relevant concentrations, acts directly on neural precursor

cells to enhance their survival both *in vitro* and *in vivo*[62]. This action of Cyclosporin A is promising for the development of regenerative strategies which aim to repair and regenerate damaged or diseased Central Nervous System tissue**.** It has been shown to block mitochondrial permeability transition pores which in open state causes mitochondrial dysfunction and preservation of mitochondrial function assessed by tissue oxygen consumption, directly translated into improvements in motor and cognitive behavior[63]. At higher doses the Cyclosporin A as well as Tacrolimus have been shown to markedly decrease expressions of Cytochrome C, AIF, caspase-3 and inhibited apoptosis pathways. It has also been shown that CsA treatment against spinal cord hypoxia induced damage is mediated via their antioxidant actions[64], i.e. it can also act as antioxidant. Tacrolimus has also been shown to be neuroprtective in case of ischemic brain damage[65]. Although the CsA has shown promise in preclinical studies but in the clinical settings failed to replicate the results. In patients with acute traumatic brain injury who received cyclosporine administered intravenously, with treatment initiated within 8 hours of injury, the rate of mortality or other adverse events was not significantly different from that of the placebo group[66]. Tacrolimus has also shown neuroprotective activity in non human primates[67].

3. Antidepressants and Mood stabilisers:

Mood stabilizers, atypical anti-psychotics and anti-depressants have been reported to have delayed therapeutic effects taking few weeks to months to exhibit their efficacy[68]. This suggests that adaptive changes in cellular signaling cascades may underlie their therapeutic effects[69-71]. Mood stabilizers are known to activate the intracellular MAPK/ERK (mitogen activated protein kinase & extracellular signal-related kinase) signaling pathway[72-74] which is used by neurotrophins, neurotransmitters, and neuropeptides to exert their effects by increasing progenitor cell proliferation and differentiation, neuronal growth, regeneration, and survival, with long-term synaptic remodeling and plasticity[75-78]. The detailed discussion of MAPK/ERK pathway is beyond the scope of this review. Valproate primarily an anti-psychotic agent and also a mood stabilizer leads to activation of the ERK pathway which can be seen in primary cortical neurons[79], cerebral progenitor cells[80], hippocampal progenitor cells[81]. Atypical antipsychotics attenuate both cognitive and non-cognitive behavioral impairments in different animal models of neurotoxicity[82-84]. Their beneficial behavioral effects are not only related to their dopamine and serotonin receptor blockade effects, but also to their effects on neuroprotection, neurotrophins and neurogenesis which require further exploration. Among anti-depressents the SSRI fluoxetine prevents the neurotoxicity[85] which may involve MAPK and BDNF[86]. MAOIs protect against dopaminergic neural toxicity[87] & Ladostigil, a MAOI has promising neuroprotective effects, owing to activation of Bcl-2 & BDNF[88]. Early and long-term effects by these agents will guide next generation of therapeutics.

4. Antiepileptics :

There has been a growing interest in the use of antiepileptic drugs (AEDs) for neuroprotection. Voltage-gated sodium channels contribute to the development of axonal degeneration in white matter tracts, so sodium channel blocking drugs can have a protective effect on injured white matter axons. Neuronal injury results due to accumulation of calcium within injured neurons and their axons due to reverse operation of the Na-Ca exchanger, that is triggered by an increase in intracellular sodium due to sodium influx via persistently activated voltage-gated sodium channels[89-90]. Pharmacologic blockade of voltage-gated sodium channels can prevent axonal degeneration and preserve function after a variety of insults to axons. Levetiracetam is found to be neuroprotective in clinically relevant animal models of subarachnoid hemorrhage & closed head injury[91]. Levetiracetam may be a therapeutic alternative to phenytoin following acute brain injury in the clinical setting when seizure prophylaxis is indicated[92-93]. Topiramate is shown to prevent excitotoxic brain damage[94] hence can be considered as a candidate therapy for neuroprotection. Phenytoin provides neuroprotection and improves functional outcome after experimental spinal cord injury[95], and warrants further exploration as a potential treatment strategy in clinical setting. So these are the potential neuroprotective antiepileptic drugs which can be exploited for the same purpose.

5. Anti-inflammatory agents :

Overexpression of COX-2 appears to be both a marker and an effector of neural damage after a variety of acquired brain injuries, and in natural or pathological aging of the brain. COX-2 expression is increased for prolonged periods in brain regions specifically associated with functional deficits after neurotrauma[96]. COX-2 has been associated with worse outcomes after brain injury, as well as early onset dementia[97]. COX-2 inhibitors may be neuroprotective in the brain by reducing prostanoid and free radical synthesis, or by directing arachidonic acid down alternate metabolic pathways.

Inhibition of COX-2 after pathological insult has been shown to benefit recovery in the brain and spinal cord[98]. COX-2 inhibitors are potent neuroprotectants in vitro and in vivo. Inhibition of COX-2 protected neurons in mixed cultures against N-methyl D-Aspartate (NMDA) excitotoxicity[99].

Minocycline, a tetracycline antibiotic, & has demonstrated neuroprotective qualities in experimental models of CNS trauma, stroke, spinal cord injury, and neurodegenerative diseases. Recent studies have focused on the anti-inflammatory[100,101] & antiapoptotic[102,103] properties of minocycline. Minocycline in human trials of stroke[104] and spinal cord injury[105] has shown positive results, but further study is warranted in order to draw a handsome conclusion.

Further interleukin-1 receptor antagonist (IL-1ra) is an important anti-inflammatory cytokine which blocks all known actions of IL-1 showing potent, sustained, neuroprotective effects[106]. In experimental models of TBI, IL-1 receptor following trauma contributes to the pathology and that antagonism can reduce both anatomical and functional consequences of neuroinflammation[107]. A randomised phase II study of interleukin-1 receptor antagonist in acute stroke patients was undertaken showing its biological activity relevant to the disease process and its clinical outcome indicated by a greater proportion of patients receiving rhIL-1ra with minimal or no disability at 3 months compared with placebo[108] so it's a potential new therapeutic agent for neuroprotection. Beside antithrombotic property Aspirin also has direct neuroprotective effects because of inhibition of glutamate release via recovery of ATP levels[109] and inhibition of serotonergic activity[110]. It also inhibits glutamate-mediated induction of nuclear factor kappa B which is an anti-inflammatory action which may contribute indirectly to neuroprotection[111]. Prostaglandin E_2 EP1 receptors are essential for the neurotoxicity mediated by COX-2–derived prostaglandin E_2. EP1 receptors disrupt Ca^{2+} homeostasis by impairing Na^{+}-Ca^{2+} exchange, a key mechanism by which neurons cope with excess Ca^{2+} accumulation after an excitotoxic insult[112]. Subsequent increase in intracellular calcium concentration is an important factor for excitotoxic death ultimately contributing to neuronal death[113]. Microglial modulation of neuronal excitotoxicity through interaction with the EP1 receptor and may have important role in neuronal injury as microglia are associated with neuronal injury[114]. So EP1 receptor inhibition may be a potentially valuable strategy for neuroprotection that deserves further investigation.

6. Anti-apoptosis agents :

Apoptosis classically defined as Programmed cell death which is a highly complex process and discussion of its mechanism is beyond the scope of review. Caspases, or *c*ysteine-*asp*artic prote*ases* or cysteine-dependent aspartate-directed proteases are a family of cysteine proteases that play essential roles in apoptosis, necrosis, and inflammation[115]. Activation of microglia and inflammation-mediated neurotoxicity are suggested to play a decisive role in the pathogenesis of several neurodegenerative disorders. Activated microglia release pro-inflammatory factors that may be neurotoxic. Caspase-8 and caspase-3/7 are involved in regulating microglia activation and inhibition of these caspases could be neuroprotective[116]. Caspase-3 contributes to delayed cell death and brain injury after neonatal hypoxia-ischemia and that calpain activation is associated with and likely a marker for the early component of excitotoxic/necrotic brain injury[117]. Olesoxime is a cholesterol-oxime compound family of mitochondrial pore modulators[118] having cholesterol-like structure and exhibits potent neuroprotective properties in preclinical studies by promoting the function and survival of neurons through interactions with the mitochondrial permeability transition pore (mPTP)[119]. Presently Olesoxime is undergoing a phase II clinical trial as treatment for spinal muscular atrophy[120]. The calpains are calcium-dependent intracellular proteases that are activated in a number of pathogenic conditions. The proposed physiologic roles of calpains in the brain include regulation of neurite outgrowth[121], long term potentiation[122], and synaptic remodeling[123]. A bimodal increase in activity of calpain has been observed after brain ischemia, transient at 1 hour, peak activity at 24-48 hours with continuous increase in number of neurons showing calpain activity[124]. Targeting those intracellular processes,represents a viable therapeutic strategy for limiting neurological damage after ischemia as indicated by cell-penetrating calpain inhibitor when administered systemically[125]. Leupeptin, also known as *N*-acetyl-L-leucyl-L-leucyl-L-argininal, is a naturally occurring protease inhibitor that can inhibit cysteine, serine and threonine peptidases. Both calpain inhibitor I and leupeptin protected neurons against ischemic and hypoxic damage i.e they are neuroprotective as indicated by increased cell viability and protein content in the cultures, and fewer damaged neurons in the hippocampal CA1-subfield[126]. The nuclear enzyme poly(ADP-ribose) polymerase (PARP) has been shown to be activated following traumatic brain injury (TBI), binds to DNA strand breaks and utilizes nicotinamide adenine dinucleotide which can lead to cell injury via severe, irreversible depletion of the NAD and ATP pool, and PARP-1 inhibitors have been expected to rescue neurons from degeneration in a number of disease models[127].

7. Excitotoxicity:

Glutamate is supposed to be involved in an acute excitotoxic process that occurs immediately after ischaemic or traumatic injury but, after this early time period, glutamate may then resume its normal physiological functions, including facilitation of neuronal survival. NMDA (N-methyl-D-aspartate) receptor targeting drugs developed as neuroprotective agents, specifically selective NMDA receptor antagonists, have not been effective in large randomised controlled trials of adequate methodological quality for most selected indications, primarily ischaemic stroke and traumatic brain injury[128]. The drugs that completed trials included antagonists of the glutamate site (selfotel)[129] and the glycine site (gavestinel)[130], an antagonist of the ionchannel site (aptiganel)[131], and an NR2B subunit-selective antagonist (traxoprodil)[132]. Recently, increasing evidence based on molecular studies suggests that memantine, an uncompetitive NMDA receptor blocker with fast channel unblocking kinetics to prevent it from occupying the channels and interfering with normal synaptic transmission, is a potent neuroprotectant[133]. As a neuroprotective agent, memantine can reduce functional as well as morphological sequelae induced by ischemia[134].

Glutamate carboxypeptidase II (GCPII), also known as N-acetyl-L-aspartyl-L-glutamate peptidase I (NAALADase I), NAAG peptidase, is a zinc metalloenzyme that resides in membranes, which catalyzes the hydrolysis of N-acetylaspartylglutamate (NAAG) to glutamate and N-acetylaspartate (NAA)[135-136]. NAAG is one of most commonly found neurotransmitters the central nervous system[137]. Glutamate is a common and abundant excitatory neurotransmitter in the central nervous system; however excess of glutamate transmission, can damage neurons due to excitotoxicity and has been implicated in many neurological diseases and disorders[137]. NAALADase inhibitor 2 (phosphonomethyl) pentanedioic acid (2-PMPA) has shown efficacy in protecting neurons against injury caused by cellular anoxia[138]. NAALADase inhibition may represent a novel glutamate regulating strategy devoid of the side-effects that have hampered development of postsynaptic glutamate receptor antagonists. A lead NAALADase inhibitor termed GPI 5693 in phase I clinical testing was found to be safe and tolerable in healthy subjects[139].

AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor are both glutamate receptors and cation channels which are important to plasticity and synaptic transmission. Modifications in AMPA receptors at the postsynaptic membrane cause changes in synaptic strength, and is a key regulator of various forms of synaptic plasticity. Thus, enhancing the activity of AMPA receptors has been shown to increase production of certain growth factors[140] and to regulate the mechanism of neurite growth[141]. The agents which positively modulate the activity of AMPA receptors can be exploited to treat a variety of neuropsychiatric disorders.

Dexanabinol is a synthetic cannabinoid derivative which does not act as a cannabinoid receptor agonist, instead act as NMDA receptor antagonist[142]. It is anticonvulsant and neuroprotective, and is implicated in studies for treatment of head injury[143]. It was shown to be safe in clinical trials[144].

8. Erythropoietin (EPO) :

EPO is made locally in response to injury or metabolic stress as a protective factor in brain, spinal cord, or heart[145]. A large body of experimental evidence suggests that rhEPO is neuroprotective after different types of cerebral tissue injuries such as ischemia[146] or traumatic brain injury[147]. The protective effects of rhEPO were associated with a decrease in the number of apoptotic neurons[148] and an increase in the expression of the anti-apoptotic bcl-2 gene[149]. A recent retrospective study in patients with severe TBI, showed that administration of rhEPO was associated with a significantly lower in hospital mortality in comparison to match cases controls[150]. A large phase II trial, initially conducted to study the effects of rhEPO in critically ill patients as an erythropoietic agent, demonstrated in a post hoc subgroup analysis demonstrated that weekly administered subcutaneous rhEPO significantly decreased mortality in the trauma subgroup[151] .rhEPO administration after TBI may be neurorestorative[152] by enhancing neurogenesis and also probably by affording vascular protection, thereby promoting the creation of vascular niches for neurogenesis.

9. *α 2 Agonist :*

Dexmedetomidine has shown neuroprotective property in a many in vivo and in vitro studies[153], however, the mechanism of neuroprotection remains unclear and may involve Modulation of pathways leading to excitatory cell death and apoptosis. Clinical trial for assessing safety in TBI patients abandoned[154].

10. Davunetide :

Activity-dependent neuroprotective protein (ADNP) differentially interacts with chromatin to regulate essential genes. NAP is a peptide derived from ADNP that interacts with microtubules and provides potent neuroprotection[155]. Phase 2 trials are being carried out[156].

11.*Neurosteroids:*

Naturally occurring neurosteroids are potent allosteric modulators of the GABA receptor and through augmentation of this receptor function can protect neuronal cells against NMDA over activation, ischemia and TBI[157]. Progesterone appears to exert its neuroprotective effects in TBI by protecting or rebuilding the BBB, decreasing the development of cerebral edema, down-regulating the inflammatory cascade, and limiting cellular necrosis and apoptosis[158]. Recognition of the neuroprotective potential of progesterone has recently led to the completion of a clinical trial named "ProTECT" (progesterone for traumatic brain injury (TBI), experimental clinical treatment), this trial tested the usefulness of progesterone as treatment for moderate to

Severe TBI[159] The patients in the moderate TBI group given progesterone tended to have better functional outcomes, although progesterone had no effect on the disability of severe TBI survivors at the 30-day time point.

Reduced levels of estradiol have been shown to compromise the functioning and survival of neurons and to result in alterations in memory processes[160]. In the brain, the synthesizing enzyme aromatase plays a very important role in neuroprotection. Males as well as females are sensitive to the protective effects of estrogen, as estradiol has been shown to prevent ischemia-induced learning disability and neuronal loss in both sexes. Some of the neuroprotective effects of androgens are mediated by their conversion to estrogens. However, androgens also exert neuroprotective and neuroregenerative effects on their own.

This outline shows that the major groups of steroid hormones exert pleiotropic effects in the nervous system and influence the viability and regenerative capacity of neurons.

There exists a variety of other classes of drugs exist which we haven't discussed in this review, alternatively some novel non-pharmacological approaches are also there which are worth mentioning e.g. Oxygen carriers, hypothermia, exercise, trans-cranial magnetic stimulation etc. The use of a particular approach after TBI depend on patient's status and varies from patient to patient. Since the newer aspects of mechanism of conventional drugs are being elaborated this will boost our approach to look for neuroprotective agent.

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