Advances in Neurotherapeutic Delivery Technologies

Edited by
Viness Pillay*
Yahya E Choonara
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Introduction

Diseases of the nervous system range from the paroxysmal disorders, namely epilepsy, migraine and the affective illnesses to the degenerative disorders including Alzheimer's disease, Parkinson's disease and Motor neurone disease. There are many categories and classifications that are now standard. The Global Burden of diseases report by the WHO estimated that 6.2 million people die because of stroke each year, 50 million people have epilepsy and 35.6 million people suffer dementia [1]. The prevalence of migraine is more than 10% worldwide.

From 1990 to the end of 1999, the Library of Congress and the National Institute of Mental Health of the National Institutes of Health sponsored a unique interagency initiative to advance the goals set forth in a proclamation by President George Bush designating the 1990s as the Decade of the Brain: “to enhance public awareness of the benefits to be derived from brain research” through “appropriate programs, ceremonies and activities.” The US National Institutes of Health remained the largest source of funding, with a 1999 budget for brain disorders that exceeded $3 billion [2].

To address this large and increasing burden, activities need to be undertaken to focus on prevention, diagnosis and treatment of neurological disorders. The extension of life expectancy and the ageing of the general populations in both developed and developing countries are likely to increase the prevalence of the many chronic and progressive physical and mental conditions.

Neurological Treatment

The hallmark of neurological diseases that makes them complex and intriguing is that they are defined by symptoms that are common and non-distinguishable. Headaches can be due to migraine or brain tumours. Hemiplegias can be caused by strokes, brain tumours, multiple sclerosis and migraine. Seizures are caused by focal brain lesions, infections, metabolic derangements and epilepsy.

The treatment of neurological disorders is therefore largely non-specific. Similar treatment
modalities are utilized for a multitude of disorders. This non-specificity of treatment presents the first major challenge in neurological therapeutics.

Neurological treatment modalities may be broadly divided into:

1. Immunological
2. Neurochemical
3. Electrical
4. Surgical
5. Rehabilitative

**Immunological**

The advent of corticosteroids in 1944 and their subsequent widespread use in neurological disorders long preceded recent advances in the complex understanding of neuropharmacology and neuroimmunology. Corticosteroids have potent anti-inflammatory and immunosuppressive properties by their effect on cytokines, chemokines, inflammatory enzymes and adhesion molecules [3]. They have potent inhibitory effects on pro-inflammatory gene transcription by activating a specific cytoplasmic receptor which then migrates to the cell nucleus and interferes with transcription factors NF-κB and AP-1. This is achieved by increasing the compaction of unwound chromosomal DNA in a process that involves deacetylation of histone proteins. The net result includes inhibition of the genes that code for the cytokines IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8 and IFN-γ [4].

Their primary anti-inflammatory mechanism is lipocortin-1 synthesis, which blocks eicosanoid production, as well as inhibits various leukocyte-mediated inflammatory events (epithelial adhesion, emigration, chemotaxis, phagocytosis, and the respiratory burst).

It is the pleiotropic effects of corticosteroids that have led to them often being used on an empirical basis in a wide variety of neurological diseases. These include immune-mediated diseases such as Multiple Sclerosis and Myasthenia Gravis, inflammatory diseases such as neurosarcoidosis, infections such as meningitis, and in the management of malignancies such as lymphoma and primary brain tumours.

The widespread effects of corticosteroids come at the cost of significant widespread systemic side-effects including gastritis, hypertension, osteomalacia, steroid-induced diabetes mellitus and numerous other metabolic and endocrine disturbances. These side-effects commonly necessitate dosage limitation and preclude prolonged usage, despite a good clinical response to the disease being treated [3].

An alternative modality of immunomodulation involves the infusion of Intravenous Immunoglobulins (IVIG). These agents utilize multiple mechanisms of action, including effects on B-cells, T-cells, the complement system, macrophages, cytokines, cell migration and superantigens [5]. IVIG has proven efficacy in neurological diseases such as Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) and Myasthenia Gravis (MG) [6].

Plasma exchange is another immunomodulatory modality which involves the removal of antibody-rich plasma and replacement with donor plasma or albumin. The removal of the offending antibodies is effective in the treatment of immune-mediated diseases such as AIDP, MG and Neuromyelitis optica [7].

An illustration of the treatment dilemmas faced by clinicians with regards to non-specificity of treatment is in the management of Neuromyelitis optica (NMO). This is an inflammatory demyelinating disease of the Central Nervous System (CNS) with a predilection for the spinal cord and optic nerves [8]. Patients with NMO are often severely disabled by
their visual loss and limb paralysis. The disease is strongly associated with antibodies to Aquaporin-4, the predominant water channel in the CNS. The presence of these antibodies in the serum has been reported to be up to 100% specific for NMO [9]. However, despite the clear identification of the pathogenic antibody, there are currently no modalities of treatment to specifically target these antibodies. Instead, treatment revolves around non-specific immunomodulation using corticosteroids, plasma exchange and other immunosuppressant agents such as Azathioprine and Methotrexate [8].

Myasthenia Gravis (MG) is an autoimmune disease of the neuromuscular junction resulting in fluctuating weakness of the extraocular muscles, bulbar muscles and systemic weakness. Acetylcholine (ACh) is the principal neurotransmitter of the neuromuscular junction, utilizing nicotinic receptors. Antibodies to the acetylcholine receptor on the postsynaptic membrane result in destruction of these receptors, and are implicated in the pathogenesis of MG. Other antibodies implicated include those to Muscle Specific Kinase (MuSK) and the low-density Lipoprotein Receptor-Related Protein (LRP4) [10].

The pharmacological management of MG is focused on immunomodulation. As in the case of NMO, in spite of the presence and identification of a specific offending antibody, the immunotherapy of these diseases continues to centre on “blanket” treatments with non-specific agents such as corticosteroids, IVIG and plasmaphoresis [11]. The link between identifying the antibody and directly targeting it remains a major therapeutic challenge.

**Neurochemical**

These treatments are targeted at either neurotransmitters or ion channels.

**Neurotransmitter-based therapies:** Neurotransmitters are endogenous chemicals which transmit signals across the synaptic cleft. The major neurotransmitters in the nervous system are either amino acids (glutamate, GABA and glycine) or amines (acetylcholine, dopamine, serotonin, adrenaline and noradrenaline).

Glutamate is the principal excitatory neurotransmitter in all parts of the Central Nervous System (CNS), while GABA (and glycine in the spinal cord) performs the major inhibitory role. Acetylcholine (ACh) is the chief neurotransmitter of the peripheral nervous system, and is also used in the nuclei of the reticular formation of the brainstem as well as the basal forebrain with projections to the cerebral cortex. Dopamine (DA) is used by neurons in the hypothalamus, substantia nigra, limbic system and prefrontal cortex. Serotonin, adrenaline and noradrenaline are produced in brainstem nuclei and act predominantly on brainstem neurons with long branching axons extending their effects to all parts of the CNS [12].

Abnormalities in these neurotransmitter systems often manifest as clinical diseases of the central or peripheral nervous systems.

As described earlier, destruction of post-synaptic ACh receptors is thought to be responsible for MG. Temporary symptomatic relief from MG symptoms is obtained by increasing the amount of ACh available in the synaptic cleft. This is achieved by inhibition of acetylcholine esterase, the enzyme responsible for ACh degradation, using drugs such as pyridostigmine [11,13].

Unfortunately the increase in synaptic ACh results in significant peripheral side-effects due to its action on muscarinic receptors. These side-effects, such as diarrhoea, abdominal cramps and excessive salivation are significant dosage-limiting factors [13]. The ideal therapeutic agent would involve the exclusive targeting of nicotinic receptors, thus avoiding the side-effects associated with muscarinic stimulation. It is this inability to deliver drugs to specifically targeted sites which poses another major obstacle in the management of neurological diseases.

These challenges with targeted drug delivery to a defective neurotransmitter system
are also apparent in neurodegenerative diseases such as Alzheimers Disease (AD) and Parkinsons Disease (PD).

AD is responsible for 60% of the 24 million cases of dementia worldwide [14]. It is characterized by gross cerebral atrophy, indicative of neuronal loss, with numerous extracellular neuritic amyloid plaques and intracellular neurofibrillary tangles found predominantly in the frontal and temporal lobes, including the hippocampus [15].

The cholinergic hypothesis proposes that a deficiency of ACh in the cerebral cortex is partially responsible for the symptoms. Potentially promising treatment options with acetylcholinesterase inhibitors have been largely disappointing in clinical practice. Similarly, treatment with antioxidants, amyloid-targeted drugs, nerve growth factors, c-secretase inhibitors and vaccines against amyloid has failed to satisfactorily attenuate disease progression [16].

PD is as a result of degeneration of dopaminergic neurons in the midbrain, resulting in a reduction in brain Dopamine (DA) levels. The clinical hallmarks include bradykinesia, rigidity and resting tremor [17]. The mainstay of current medical management is the oral administration of levodopa, the precursor of dopamine. Other drug categories, including DA receptor agonists, COMT-inhibitors and MAO-B inhibitors are generally considered to be adjunctive treatment to levodopa, or alternatively may occasionally be used as monotherapy in very mild disease. None of these drugs have shown convincing superiority over levodopa [17,18].

Due to the pharmacokinetic challenges posed by oral levodopa administration, alternative routes of delivery of drugs in PD are attracting increasing interest. These include direct administration of levodopa into the duodenum via a surgically-implanted automated pump, subcutaneous apomorphine (a DA receptor agonist), and transcutaneous delivery of rotigotine via adhesive skin patches. Current evidence has failed to show superiority of any of these modalities over oral levodopa, however the slightly more favourable side-effect profile is a promising development [17,18].

The concept of neuroprotective therapeutics in PD has been brought to the fore with some promising data on the MAO-B inhibitor Rasagiline. However whether or not this apparent neuroprotective effect will manifest in any significant improvement in patient outcomes remains to be seen [19].

Other neurological diseases associated with neurotransmitter abnormalities range from migraine and depression (serotonin dysregulation), to epilepsy and stiff-person syndrome (GABA dysregulation), further illustrating the widespread effects of abnormalities of the neurochemical systems.

**Ion channel-based therapies:** The neuronal membrane is composed of a lipid bilayer of high electrical resistance, thus inhibiting the flow of ions. An ion channel is a complex protein macromolecule which spans the neuronal membrane, allowing the rapid passage of ions from one side to the other.

Opening and closing of these channels may be mediated either by electrical changes (voltage-gated channels) or by the binding of neurochemicals (ligand-gated channels). Voltage-gated channels are named for the ion species to which they are most permeable, including sodium, potassium, calcium and chloride, each of which have numerous subtypes [20].

Ion channels form the molecular basis for intracellular signal transduction, maintenance of the resting potential and the generation of excitatory and inhibitory potentials. It is thus plausible that abnormalities in these channels may have widespread neurological consequences. However it has not been until the last two decades that such diseases are being identified as having their origins in defective ion channel functioning.
Abnormalities in ion channels are now gaining increasing importance in a variety of neurological conditions, including epilepsy, pain syndromes and the relatively recent recognition of a group of disorders called the channelopathies. These include diseases such as Periodic paralysis, Familial hemiplegic migraine and Episodic Ataxia. Numerous distinct inherited mutations in the calcium, potassium, sodium and chloride ion channels have been implicated in different disease processes [21].

The pharmacological management of these disorders revolves around modulation of these abnormal ion channels. For example, Phenytoin is a commonly used anti-epileptic agent which exerts its effect by inhibition of voltage-gated sodium channels, and to a lesser extent, inhibition of calcium channels [22]. Phenytoin is also effective in the management of the symptoms of Myotonia congenita, a channelopathy involving abnormal chloride channels. Other drugs also used for this purpose include quinine (an antimalarial agent) and procainamide (an anti-arrhythmic drug) [23].

This illustrates that despite the clear identification of the mutated channel, there is currently a deficiency in therapeutics which are able to be specifically targeted to the abnormal channel, without having systemic effects on other channels and systems.

It is likely that many more diseases will be identified to have ion channel abnormalities as their underlying pathology, which will lead to this category of neurological diseases vastly expanding in the future. The development of more targeted therapeutics to the specific channel pathology is a definite requirement.

**Electrical Treatment**

Electrical treatment includes deep brain stimulation, vagal nerve stimulation and transcutaneous nerve stimulation.

**Deep Brain Stimulation (DBS):** DBS involves implanting electrodes in various areas in the brain, producing electrical impulses to regulate abnormal impulses or assists neurons in releasing neurotransmitters. It has been used successfully in treating various neurological illnesses and is the most frequently performed surgical procedure for the treatment of advanced Parkinson's Disease (PD). Randomised controlled studies have confirmed that stimulation of the subthalamic nucleus and globus pallidus interna not only reduces the tremor and bradykinesia in PD but also alleviates the motor fluctuations and dyskinesias associated with advanced PD thereby reducing the need for antiparkinson drugs [24]. Low quality evidence suggests using DBS to alleviate other hyperkinetic movement disorders (dystonias and dyskinesias) refractory to oral pharmacologic therapy or botulinum toxin injections [25,26]. DBS has been successful in treating Essential Tremors (ET) involving limbs; however there is limited and conflicting data regarding the use of DBS for head tremor and voice tremor in ET [27]. Although neuromodulation of the brain to achieve analgesia is in its infancy, anecdotal reports of DBS and motor cortex stimulation have been described for the treatment of intractable severe persistent pain states [28].

**Vagal Nerve Stimulation (VNS):** VNS is considered a valid treatment option for adults and older children with medically-refractory epilepsy who are not candidates for, or whose seizures persist after, resective epilepsy surgery. Data on the efficacy of VNS in younger children is conflicting. One study found no benefit of VNS compared with low-stimulation control in patients 3 to 17 years in age [29]. Other open-label studies suggest that younger children and individuals with other epilepsy syndromes (eg, Lennox Gastaut syndrome) might benefit from VNS [30].

**Transcutaneous Nerve Stimulation (TNS):** Data for TNS is limited but treatment of migraines with a supraorbital transcutaneous electrical nerve stimulator has been successful [31]. There are inconsistent data from small randomized trials regarding the benefit of occipital nerve stimulation for the treatment of chronic migraine [32,33].
Neurosurgical Treatment

Neurosurgical interventions for neurological diseases are most relevant with treatment of medically refractive epilepsies. Surgical procedures for epilepsy range from focal resection of the epileptogenic cortex (antero-mesial temporal lobe and other focal cortical resections) to interventions that remove or isolate the cortex of a grossly diseased hemisphere (functional hemispherectomy, anterior corpus callosotomy, multiple subpial transections). Surgical therapy is an effective and underutilized treatment for medically refractory focal seizures in adults. The most common surgical procedure for medial temporal epilepsy is resection of the anterior temporal pole, hippocampus and part of the amygdala. Selective amygdalohippocampectomy has been explored as an alternative to anterior temporal lobectomy that spares the temporal lobe neocortex. Low grade primary brain tumors, vascular malformations and malformations of cortical development are other causes of refractory focal epilepsy. Resection of the epileptogenic brain region often results in improved seizure control.

Neurological rehabilitation

The quality of life of a person can be greatly affected by neurological disease. Many skilled professionals are part of the neurological rehabilitation team, including physiotherapists, occupational therapists, psychologists and speech and language therapist/audiologist. The goal of neurological rehabilitation is to help the patient return to the highest level of function and independence possible, while improving the overall quality of life - physically, emotionally and socially.

In order to help reach these goals, neurological rehabilitation programs may include the following:

- Assistance with Activities of Daily Living (ADLs), such as eating, dressing, bathing, toileting, handwriting, cooking, and basic housekeeping
- Speech therapy to help patients with speaking, reading, writing, or swallowing
- Stress, anxiety, and depression management
- Bladder and bowel retraining
- Activities to improve mobility, muscle control, gait, and balance
- Exercise programs to improve movement, prevent or decrease weakness caused by lack of use, manage spasticity and pain, and maintain range of motion
- Activities to improve cognitive impairments, such as problems with concentration, attention, memory, and poor judgment
- Help with obtaining assistive devices that promote independence
- Patient and family education and counselling
- Safety and independence measures and home care needs
- Pain management

Challenges in Neurotherapeutics

It is clear from the description above that the major challenge in neurological treatment is the failed expectancy of the treatments regimens currently in place.

The major reasons for this lie as discussed above in the non-specificity of the treatments but other factors rest with pharmacodynamics and pharmacokinetics. The main issues in this regard are site of delivery, interactions with proteins, degradation in the blood, and...
perhaps the biggest challenge of all passage across the barriers to reach the specific sites in the brain.

Many potential drugs, which are effective at their site of action, have failed and have been discarded during their development for clinical use due to a failure to deliver them in sufficient quantity to the CNS. The first obstacle an oral drug encounters is in the Gastrointestinal Tract (GIT) i.e., the Blood- GIT barrier. Once absorbed in the GIT, the delivery of drugs to the CNS via the cardiovascular system is often prohibited by formidable barriers including the Blood-Brain Barrier (BBB) and the Blood-CSF Barrier (BCB).

**Blood-GIT barrier**

The absorption of an oral drug in the gastrointestinal tract is a key component to achieving good bioavailability and ensuring the drug is able to reach the systemic circulation. Drug absorption predominantly occurs in the small intestine where the presence of villi and microvilli greatly increase the surface area for optimal absorption. Drug absorption here is also greatly influenced by multiple interacting factors, including drug properties (solubility, formulation, concentration, etc.), gastrointestinal properties (pH, food intake, region of the small intestine, etc.), metabolism, permeability and active transport across the intestinal epithelial membrane.

Levodopa is an amino acid which is the gold standard drug in treatment of Parkinson’s disease. Due to its peculiar pharmacokinetics, plasma levodopa concentrations fluctuate widely and thus obtaining an optimal therapeutic regimen with levodopa is difficult [34]. Factors complicating the pharmacokinetics of levodopa include:

- Metabolism of levodopa to dopamine in the gut: This results in only 30% of the levodopa dose reaching the systemic circulation, necessitating the need to administer levodopa in combination with carbidopa or benserazide to prevent this presystemic metabolism.

- The narrow absorption window at the upper part of the small intestine: This implies that gastric emptying determines the rate and the extent of its absorption. If gastric emptying is delayed, levodopa may be erratically absorbed, resulting in slower relief of symptoms and “on-off” fluctuations. Some factors potentially interfering with gastric emptying and affecting levodopa bioavailability include meals, caffeine, exercise and drugs like anticholinergics.

- Rapid intestinal absorption by a saturable facilitated transport system: Aromatic and branched chain amino acids of concomitant protein meals may compete with levodopa for the carrier system across the intestinal mucosa directly affecting levodopa absorption.

**Blood-Brain Barrier (BBB)**

The BBB is the Achille’s heel for treating virtually all neurological disorders. It is a specialized system of cells that acts as a natural gatekeeper for the brain from the circulating blood, blocking harmful substances from entering while allowing in necessary nutrients. In this neuroprotective role the BBB and the blood-CSF barrier hinder the delivery of many potentially important diagnostic and therapeutic drugs to the CNS. The exchange of substances between brain tissue and blood is restricted by both physical (tight junctions) and metabolic (enzymes) barriers. For a molecule to be able to cross the BBB it has to be lipophilic and have a molecular weight of <400Da. Most small molecules lack these dual molecular characteristics, thus do not cross the BBB [35]. Sedatives like diazepam are lipophilic and readily cross the BBB whereas cyclosporin, an immunosuppressive drug designed to prevent rejection in organ transplantation patients, and became popular for the treatment of myasthenia gravis in the 1990s is more lipophilic than diazepam but does not readily cross the BBB. By the same token, the lack of penetration of majority of the chemotherapeutic drugs, even though lipophilic, leads to difficulty in the treatment of brain tumours. On the other hand, levodopa (197Da), used to treat Parkinson’s disease, is very
hydrophilic, but can readily penetrate the BBB. Of the more than 7000 molecules in the Comprehensive Medicinal Chemistry (CMC) database, <5% of all drugs are active in the CNS and the activity of these drugs is generally confined to just four conditions: affective disorders, chronic pain, insomnia and epilepsy. If affective disorders are excluded, <1% of all drugs are pharmacologically active in the brain. The BBB problem is much worse in the case of large molecule drugs. Essentially 100% of macromolecular drugs do not cross the BBB, including all of the products of biotechnology: recombinant proteins and enzymes, Monoclonal Antibodies MAb), antisense drugs, short interfering RNA (siRNA), or gene therapy [35].

Neurological Illnesses with BBB abnormalities: Epilepsy is a common neurological disease that is characterized by a tendency for recurrent seizures. Research has implicated that breakdown of the BBB may trigger chronic or acute seizures. Inflammatory mechanisms may participate in the pathological changes observed in epileptic brain, with increasing awareness that blood-borne cells or signals may participate in epileptogenesis by virtue of a leaky BBB [36].

Multiple sclerosis is an autoimmune disease, in which the immune system launches a defensive attack against nerve-insulating myelin. MRI studies have shown disruption of the BBB during an MS relapse, allowing T lymphocytes to cross over and attack the myelin. It has sometimes been suggested that, rather than being a disease of the immune system, MS is a disease of the blood-brain barrier.

Some new evidence hypothesises that disruption of the blood-brain barrier in Alzheimer’s disease patients allows blood plasma containing amyloid beta (Aβ) to enter the brain where the Aβ adheres preferentially to the surface of astrocytes. This soluble exogenous Aβ internalises and overwhelms the astrocyte, resulting in the astrocyte dying, rupturing and disintegrating, leaving behind the insoluble Aβ plaque. Thus, in some patients, Alzheimer’s disease may be caused (or more likely, aggravated) by a breakdown in the BBB.

With meningitis, the blood-brain barrier may be disrupted. This disruption may increase the penetration of various substances (including either toxins or antibiotics) into the brain. Antibiotics used to treat meningitis may aggravate the inflammatory response of the central nervous system by releasing neurotoxins from the cell walls of bacteria - like Lipopolysaccharide (LPS).

Blood-Cerebrospinal Fluid Barrier (BCB)

The BCB is distinct from the BBB but can also prevent drugs from entering the CNS. The BCB is formed by the epithelial cells of the choroid plexus and the tight junctions that link them, and the arachnoid membrane which envelops the brain. The arachnoid membrane is generally impermeable to hydrophilic substances. In addition, the BCB is fortified by an active organic acid transporter system in the choroids plexus capable of driving CSF-borne organic acids into the blood. As a result a variety of therapeutic organic acids such as the antibiotic penicillin, the anti-neoplastic agent methotrexate, and the antiviral agent zidovudine are actively removed from the CSF and therefore inhibited from diffusing into the brain parenchyma.

Potential Solutions

Nanosystems - Nanotechnology employs engineered materials or devices that interact with biological systems at a molecular level and could revolutionize the treatment of neurodegenerative disorders by stimulating, responding to and interacting with target sites to induce physiological responses while minimizing side effects [37].

Implantable devices – Gut, Brain

An Ommaya reservoir is an intraventricular catheter system that can be used for the
delivery of drugs intrathecally (directly into the cerebrospinal fluid) thereby treating brain
tumors, leukemia/lymphoma or leptomeningeal diseases. It consists of a catheter in one
lateral ventricle attached to a reservoir implanted under the scalp. In the palliative care
of terminal cancer, an Ommaya reservoir can be inserted for Intracerebroventricular (ICV)
injection of morphine.

**Intranasal drug delivery**

Generally the nasal route has been used for delivery of drugs in the treatment of local
diseases. However intranasal drug delivery has emerged as a useful and reliable alternative
to oral and parenteral routes as the nasal cavity possesses many qualities which are
advantageous, such as a large surface area for absorption with a highly vascularised
subepithelial layer. The direct transport of absorbed drug into the systemic circulation
avoids the first-pass metabolism by the liver, bypasses the blood-brain barrier and results
in preferential absorption to the cerebrospinal fluid [38].

**Conclusion**

Neurotherapeutics remains in its infancy despite the great strides made in the past
decades. We now have more evidence and more science behind these amazingly complex
natured diseases. The maps have been drawn and the targets are there to reach.

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